Critical assessment of an FDA letter concerning a Citizen Petition specifying actions against Thimerosal-containing drugs

Paul G. King, PhD
Science Advisor and New Jersey Representative,
CoMed, Coalition for Mercury-Free Drugs
33A Hoffman Avenue
Lake Hiawatha, NJ 07034-1922

Abstract

The review that follows this introductory letter is a critical assessment of an FDA letter, date-stamped "SEP 26 2006," to **CoMeD** regarding FDA Docket Number 2004P-0349/CP1, a Citizen Petition filed seeking to compel the FDA and the Secretary of Health and Human Services to take certain actions against Thimerosal-containing drugs until the federal government can prove the safety of such Thimerosal-containing drug products in a manner that complies with **21 CFR 610.15(a)** and **42 U.S.C. 300aa-27(a)(2)**. **CoMeD** and the petition signers received the *complete* letter, which is being reviewed, at some time on 28 September 2006.

In general, to clearly differentiate between the assessment comments and those of the letter **CoMeD received**, when the letter's printed statements are quoted, they are quoted in an *italicized* "***Times New Roman***" font followed by the reviewers, remarks in indented text written in a "**News Gothic MT**" font. Quotes from general reference articles and documents will, in general, be presented in an "**Arial**" font; federal laws, statutes and court decisions will be quoted in a "**Lydian**" font.

Overall, this critical assessment established that the FDA letter failed to address the issues raised in the **CoMeD** Citizen Petition and, instead, addressed issues *not* raised in the **CoMeD** Citizen Petition—issues that the FDA created.

Keywords: Thimerosal, Thimerosal-containing drugs, adverse reactions, mercury, vaccines, poisoning, toxicity

"**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."

First, we find that your response has misstated the underlying basis for all the actions the **CoMeD** Citizen Petition requested.

Factually, **CoMeD**'s underlying bases for all of the actions we requested are:

doi: 10.1588/medver.2007.04.00145

1. The FDA's licensing and/or approval of preserved drug products that the manufacturers have *not* been proven to be safe to the extent required by **21 CFR § 610.15(a)** – "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," and
2. The Secretary of Health and Human Services' failure, through the Agencies who report to him, to comply with the clear mandate to safen childhood vaccines by reducing the risks of adverse reactions to vaccines through any and all means within the Secretary's authorities, a clear "shall" requirement set forth in **42 U.S.C. Sec. 300aa-27(a)(2)** – "General rule In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall – (1) …, (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, …"

That "lack of proof of safety" is an underlying basis for the **CoMeD** citizen petition filed under Docket Number 2004P-0349/CP1, is clearly stated in the opening of the petition on page "P-1" (with underlining added for emphasis):

"**I. Actions Requested**

Petitioners request:

1. *Until the federal government can **prove** that any and all Thimerosal-containing products have a **10X** safety margin with respect to the risk of causing any level of neurological damage in newborns and children under 36 months of age*, [1,2] we request, under **42 U.S.C. Section 300aa-27**, the **Secretary** of the Department of Health and Human Services **or** the **Acting Commissioner** of the Food and Drug Administration **to immediately issue an order** proscribing the use of disease-preventive Thimerosal-containing vaccines or other similarly preserved medical products in newborns, children under the age of 36 months, and pregnant women …"

This "proof of safety" basis is further established in the next point raised on page "P-1" of the **CoMeD** citizen petition, which states (with dashed underlining added for emphasis):

"2. *Until the federal government can **establish** that any and all Thimerosal-containing products have no less than a **10X** safety margin with respect to the risk of causing any level of neurological damage to developing fetuses, newborns, children and adolescents*, we request that the Commissioner of the Food and Drug Administration move to withdraw the approval (under **21 U.S.C. 355(e)**) of any FDA-approved drug product (*e.g.*, ophthalmic products) and revoke the license (under **42 U.S.C. 262(a)(2)(A)**) of any FDA-licensed biological product (*e.g.*, vaccines and other preserved serological preparations) that uses Thimerosal, *or any other mercury-based neurotoxic compound*, as a "preservative" or "adjuvant" unless the federal government and/or the manufacturer of said medical product **can prove, at its maximum level, its safety and efficacy as a preservative or adjuvant** in scientifically sound animal model studies using appropriate susceptible animal strains as the test subjects. [**Note:** We make this request because, *as all parties (federal government, industry, academia, and the public) know*, [3,4], **all such current products lack the appropriate safety studies**. …]"

Furthermore, your "*(t)he first part of our discussion explains how FDA came to the conclusion that those licensed and approved products are safe*" ignores the reality that under *Berkovitz v. US*,[1] *a unanimous 1988 Supreme Court case limiting administrative discretion when there is a clear policy, legal, or statutory requirement that must be met*, a drug must meet all such requirements before you can use your discretion to determine "safety" by weighing the drug's benefits *versus* its risks as you claim you are allowed to do for biological drug products using the definition of "safety" set forth in **21 CFR § 600.3(u)**, which you assert later in this letter is implicitly applicable to all drugs.

Since: **a) 21 CFR § 610.15(a)** clearly sets a minimum "proof of safety" requirement for "preservatives" in biological products which implicitly applies to all preserved drug products (just as you have implicitly held for **21 CFR § 600.3(u)**), and **b)**, *as has been repeatedly admitted by you*, the studies required to prove that preservative levels of Thimerosal or other mercury-based preservatives (*e.g.*, phenylmercuric acetate and phenylmercuric nitrate), *taken as being between "0.001% and 0.01%" by you* (based on the labeling on licensed and approved drugs where Thimerosal

[1] Kevan *BERKOVITZ*, a Minor by his Parents and Natural Guardians Arthur BERKOVITZ, et ux., et al., Petitioners, *v. UNITED STATES* **No. 87-498.** Argued April19. 1988. Decided June 13. 1988. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549 **(Cite as: 486 U.S. 531, 108 S.Ct. 1954.)**

doi: 10.1588/medver.2007.04.00145

is declared as a preservative) "shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" have *not* been conducted

We note that your letter failed to provide the requisite toxicological proofs that preservative levels of Thimerosal or other mercury-based compounds used as a preservative ("0.001% to 0.01%") are "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to" all the intended direct and indirect recipients under the worst-case dosing regimen with some appropriate safety factor as would be required to satisfy **21 CFR § 610.15(a)** in a manner that meets the scientifically sound and appropriate requirements set forth under the current good manufacturing practice (CGMP) for finished pharmaceuticals (**21 CFR Part 211)**.

Finally, though you state, "*The second part explains why the studies on which you rely do not support your contention*," we find that, *since you provide no evidence to substantiate most of your explanations and, in some cases, you failed to even accurately portray the studies you purport to be explaining*, you have failed to explain why the supportive studies upon with the **CoMeD** citizen petition relied do *not* support the evidence-based "contentions" raised by the petitioners in **CoMeD**'s citizen petition.

"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 warranted. We then explain why your claims that the government has violated people's rights lack merit and do not support your petition."

First, since you failed to

- Present substantive science to support your discussion on safety in most cases,
- Mention, much less address, the clear requirement minimums for preservatives (**see 21 CFR 610.15(a)**) that must be met before any preserved drug can be licensed or approved.
- Mention, much less address, the statutory "Mandate for safer childhood vaccines" (**42 U.S.C. Sec. 300aa-27**) that requires the Secretary to use all authorities to "reduce the risks of adverse reactions to vaccines,"

the **CoMeD** reviewers find that, *contrary to your assertion*, you have failed to address our legal arguments.

Second, given the preceding realities, we find that you have failed to:

- Establish that "*none of the legal actions or remedies*" we have sought "are warranted."
- Address the substantive issues raised in our petition.

Finally, with respect to your "*We then explain why your claims that the government has violated people's rights lack merit and do not support your petition*," we find that your explanations:

- Do *not* address the reality that the government has ***knowingly***[2]:
  - Failed to fully disclose to the recipients or their parents or legal guardians all the risks and the true risk incidences associated with each vaccine (*e.g.*, recent smallpox vaccine case where the government's claimed risk of death was 1 in 1,000,000 and, for serious harm, about 1 in 100,000, but, *as about 38,000 first providers found out*, the real rates were closer to 1 in 10,000 for deaths and 1 in 100 for severe adverse reaction),
  - Inaccurately tracked the adverse reactions to vaccines by failing to provide monetary and other sanctions for the failure of a healthcare provider to report an adverse event (*e.g.*, even the government admits that less that 10% of adverse reactions are reported to the government and entered into VAERS),
  - *Not* assessed the long-term (beyond 6 months) risks associated with each vaccine even though there is evidence that the adverse reactions for certain may occur years or decades after inoculation (*e.g.*, the development of vaccine-related diabetes and MS in children years after hepatitis B inoculation [as the French have established] "as well as causal relationship between the hemophilus vaccine and the development of insulin dependent diabetes … 3 – 4 years after four doses of Hib"[3]),
  - Understated the risks for death and serious injury from the each vaccine (*e.g.*, Varivax®)
  - Inflated the effectiveness of vaccines (*e.g.*, Prevnar®)),
  - Failed to *fully* disclose the limitations on vaccines that do *not* cover all strains of the organism for which "protection" is claimed (*e.g.*, the vaccines for Neisseria meningitidis that provide no protection for the strain

[2] **21 U.S.C. Sec. 321(bb)**, "The term 'knowingly' or 'knew' means that a person, with respect to information -
(1) has actual knowledge of the information, or
(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information."

[3] http://www.vaccines.net/newpage112.htm

doi: 10.1588/medver.2007.04.00145

that causes about 50% of the cases of disease but the government permits the manufacturers to misrepresent those vaccines a protecting those vaccinated from contracting meningitis), and
- Supported the continuing use of vaccines that, *based on government data*, are *not* effective (*e.g.*, the current human influenza vaccines),

- Are, therefore, defective on their face, and
- Have *not* established that our "rights violation" claims "*lack merit and do not support*" our 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"

We agree that the outline you provided accurately reflects your response.

"**DISCUSSION**

I. LICENSED AND APPROVED PRODUCTS ARE SAFE

A. Exposure to Mercury through Vaccines is Minimal

doi: 10.1588/medver.2007.04.00145

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]

With respect to your claim, "*A. Exposure to Mercury through Vaccines is Minimal,*" we find that, since: **a)** "*Minimal*" is defined by Webster as "of or pertaining to a minimum; smallest or least possible; as a *minimal* fraction" and **b)**, *as you have repeatedly admitted*, there is no minimum limit below which the mercury in drugs has been proven *not* to harm any human or animal, you assertion here is at best an unsubstantiated belief that we must reject because, *by law*[4], those manufacturers using Thimerosal or other mercury-based compound as a preservative are required to have conducted toxicity studies sufficient to establish that the "preservative used" is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" and submitted those studies to the FDA before, *after November 20, 1973*,[5] the FDA could lawfully license, or approve, drugs preserved with mercury-based compounds.

Until April 13, 1988, you could have argued that your administrative discretion allowed you to ignore the clear requirement set forth in **21 CFR 610.15(a)**.

However, *after April 13, 1988*, you could no longer *legally* continue to ignore this clear requirement because the US Supreme Court unanimously ruled[6] [*Berkovitz*[1]] that, when there is a clear requirement established by a federal policy, law, or statute, no administrator has the discretion to ignore the requirement.

Therefore, your failure to comply with the Supreme Court's ruling and the clear unfulfilled requirement to prove that mercury-based preservatives are "sufficiently nontoxic" bar you from making any "level" claim with respect to the exposure to mercury through vaccines.

This is the case because you have no scientifically sound and appropriate toxicology studies that have established, *as required by law*,[5] what the nontoxic level is for Thimerosal-preserved vaccines.

Thus, *for the reasons stated*, we must reject your inappropriate use of the word "*Minimal*" in your "*A*."

With respect to your initial statements, "*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*," we note that your rhetoric does *not* match your actions.

For example, with knowing disregard for **42 U.S.C. 300aa-27** and **21 CFR 610.15(a)**, the Secretary, CDC and the FDA have approved adding the Thimerosal-preserved influenza vaccine to the childhood vaccination schedule and the vaccination schedule for pregnant women without proof of nontoxicity to all who would be directly or, *in the cases of the fetuses in pregnant women*, indirectly administered such Thimerosal-preserved vaccines.

This addition of a Thimerosal-preserved vaccine to the vaccination schedule (if feasible) for pregnant women and children 6 months of age to 23 months of age in 2002 and to now (in 2006) effectively extending the vaccination age for children to 59 months of age obviously contradicts your "*FDA recognizes and supports the goal of reducing exposure to mercury from all sources*" rhetoric because you have significantly increased the exposure of fetuses and children to mercury since 2002, if *not* before.

Moreover, since the critical factor for exposure is the specific dose (dose per weight) given, you have increased the specific-dose-exposure in fetuses and young children to the point that, *if the fetus is dosed when it is large enough to survive the mercury poisoning it receives when the fetus' mother is inoculated with a Thimerosal-preserved influenza vaccine*, the specific dose administered to children today is much more than half the specific dose that children of non Rh-negative mothers in the late 1990s by age 5 and more than half the specific dose that children of Rh-negative mothers received by age 5 in the late 1990s.

Because the level of mercury exposure from vaccines is "near zero" in several European countries, we find it implausible that any prudent person would accept your contention that the FDA truly "*supports the goal of reducing*

---

4 21 CFR § 610.15(a).

5 38 FR 32056.

6 486 U.S. 531, 108 S.Ct. 1954.

doi: 10.1588/medver.2007.04.00145

exposure to mercury from all sources" when, since 2002, the maximum level of mercury exposure from vaccines has been increasing.

Because, under **42 U.S.C. 300aa-27(a)(2)**, the FDA has, since December 22, 1987, had the authority to:

- Order all manufacturers to stop using any preservative that does *not* meet the clear requirements of **21 CFR 610.15(a)**, which have been in effect since 1973, because risk of toxicity is an obvious risk of adverse reaction and
- Revoke the license of those lacking proof of nontoxicity and has, to date, *not* used that authority,

we find your "*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"* rhetoric to be both:

- Unconvincing and
- At odds with the law.

Let-1 http://www.fda.gov/ola/2002/vaccinesautism1210.html 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

"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."

We find that your assertion, "*this review found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions*," is at odds with the facts based upon, among other documents, the findings of the "**Mercury in Medicine – Taking Unnecessary Risks**" (May 2003) staff report[7] from the Subcommittee on Human Rights and Wellness, Government Reform Committee of the US House of Representatives, which was published following a three year investigation.

This report specifically stated:

> "This argument – that the known risks of infectious diseases outweigh a potential risk of neurological damage from exposure to thimerosal in vaccines – is one that has continuously been presented to the Committee by government officials. FDA officials have stressed that any possible risk from thimerosal was theoretical, that no proof of harm existed. However, the Committee, upon a thorough review of the scientific literature and internal documents from government and industry, did find evidence that thimerosal did pose a risk."[8]

Additionally, among this report's key findings were[9]:

"1. Mercury is hazardous to humans. Its use in medicinal products is undesirable, unnecessary and should be minimized or eliminated entirely.
2. …
3. Manufacturers of vaccines and thimerosal, (an ethylmercury compound used in vaccines), have never conducted adequate testing on the safety of thimerosal. The FDA has never required manufacturers to conduct adequate safety testing on thimerosal and ethylmercury compounds.
4. Studies and papers documenting the hypoallergenicity" [*sic*; hyperallergenicity] "and toxicity of thimerosal (ethylmercury) have existed for decades."

Furthermore, based upon the published results of the 1999 review by Ball *et al*.,[10] published in 2001, we find that the FDA did *not* consider the vaccine-applicable scientific evidence demonstrating Thimerosal and its ethylmercury breakdown product to be toxic in tissue culture systems, animal systems, and in humans.

Additionally, the Agency did *not*, and has yet to produce the statutory clinical or scientifically sound and appropriate toxicological evidence demonstrating Thimerosal, as a preservative in vaccines, is non-toxic to all vaccine recipients.

7 **Mercury in Medicine – Taking Unnecessary Risks**, a report prepared by the staff of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Chairman Dan Burton, May 2003. [Eighty-one page Adobe "pdf" file].

8 *ibid*., page 5.

9 *ibid*., page 7.

10 Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. ***Pediatrics***. 2001 May; **107**(5): 1147-1154.

doi: 10.1588/medver.2007.04.00145

The Congressional "**Mercury in Medicine – Taking Unnecessary Risks**" report[7] concluded, regarding the FDA's action on Thimerosal, that the FDA was, "…asleep at the switch regarding the lack of safety data regarding injected thimerosal…" and that their "…failure to act is indicative of institutional malfeasance for self-protection and misplaced protectionism of the pharmaceutical industry."

With respect to the previous review by the FDA in 1999[11] and the Ball *et al*. 2001 article, we note, *to our dismay*, that neither placed appropriate emphasis on the need to evaluate the level of harm to the fetus from the administration of Thimerosal-preserved vaccines to pregnant women.

In your entire response, you supply no evaluation or commentary to address this route of administering Thimerosal to the fetus (or for that matter from any other Thimerosal-containing or mercury-containing product administered during pregnancy).

Historically, this was a mute point because the federal government did *not* formally recommend the routine administration of any Thimerosal-containing to pregnant women until 2002.

However, *under the current vaccine recommendations*, the Advisory Committee on Immunization Practices (ACIP) and the CDC recommend that, *without regard to trimester*, all pregnant women who are pregnant during the "influenza season" are to be administered an inactivated-influenza vaccine even though most (greater than 75% for the 2006–2007 U.S. influenza season) of the inactivated-influenza vaccine doses are Thimerosal-preserved and provide a nominal 50-microgram (50,000-nanogram) dose of the highly toxic, teratogenic, and mutagenic Thimerosal (49.55% mercury) for the 0.5 mL of vaccine injected.

In our citizen petition, the **CoMeD** petitioners clearly raised the issue of protecting fetuses from exposure to mercury-containing pharmaceutical products (*i.e*. whether as Thimerosal-containing influenza vaccine or any or an over-the-counter product containing phenylmercuric acetate or nitrate as a preservative) but, *given your lack of response to this issue here*, you have apparently *knowingly* decided to ignore this important issue.

Further, previous reviews by the FDA and your present response have failed to address the issue of potential indirect infant mercury exposure from breast milk when nursing mothers are given Thimerosal-containing vaccines (or, for that matter, from any other Thimerosal-containing or mercury-containing drug) while they are breastfeeding their infant children.

Historically, studies have shown that both inorganic mercury and organic mercury compounds: **a)** are transmitted by breast milk to a developing infant and **b)** may result in neurodevelopmental disorders in children.[12]

Until the early 2000s, this was a mute point, *with respect to Thimerosal-containing vaccines*, because Thimerosal-containing vaccines were *not* recommended for routine administration to mothers who may be breast-feeding their infants.

However, under the current (2006) vaccine recommendations, the Advisory Committee on Immunization Practices (ACIP) and the CDC have recommended all mothers with young children should be given an influenza vaccine during the "influenza season."

Since many of these mothers may be breast-feeding their infants and most influenza vaccines containing full-dose Thimerosal, this recommendation now represents yet another source of unnecessary mercury exposure for infants for the children of nursing mothers who follow the government's recommendation.

The **CoMeD** petition clearly raised the issue of protecting infants from exposure to mercury-containing pharmaceutical products (*i.e*., Thimerosal-containing influenza vaccine, other Thimerosal-containing vaccine, or any other drug containing any other mercury compound as a preservative, including, but not limited to, over-the-counter products containing Thimerosal or phenylmercuric acetate or nitrate as a preservative), but we find that your response has knowingly sidestepped addressing the key aspects of this issue including the risk of harm to the fetus and nursing babies from the indirect exposure to Thimerosal-containing drugs.

Also, Special Counsel Scott J. Bloch reported (May 2004):[13]

---

[11] Center for Disease Control and Prevention. Thimerosal in vaccines: A joint statement of the American Academy of Pediatrics and the Public Health Service. ***MMWR*** 1999 July 9; **48**(26): 563-565.

[12] Amin-Zaki L, Majeed MA, Greenwood MR, Elhassani SB, Clarkson TW, Doherty RA. Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. ***J Appl Toxicol*** 1981; **1**: 210-214.

doi: 10.1588/medver.2007.04.00145

> "I have recently received hundreds of disclosures from private citizens alleging a widespread danger to the public health, specifically to infants and toddlers, caused by childhood vaccines which include thimerosal, a mercury-containing preservative…I hasten to add, however, that based on the publicly available information, as discussed briefly below, it appears there may be sufficient evidence to find a substantial likelihood of a substantial and specific danger to public health caused by the use of thimerosal/mercury in vaccines because of its inherent toxicity."

Based on all of the preceding, we must conclude that, at best, your reviews have been incomplete.

"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.

First, we note that, in 1999, the stated goal was to remove Thimerosal from all childhood vaccines and *not*, as you write here, the much weaker and more limited goal of "*removing thimerosal as soon as possible as a preservative from vaccines routinely administered to infants*."

Second we again note that, in spite of a declared goal to "decrease total mercury exposure, chiefly among infants and pregnant woman"[14] the federal government has, since at least 2002, if *not* before, raised the maximum level of Thimerosal that "infants" may receive by first recommending, "when feasible" that healthy infants 6-months to 23-months of age be vaccinated with influenza vaccines, including those that are Thimerosal preserved, during the "influenza season."[15]

Then, *in December 2003*, the Center for Disease Control and Prevention (CDC) further increased the maximum vaccine-derived mercury-poisoning burden in infants up to 23 months of age by officially recommending: **a)** these babies get two doses of vaccine, separated by a month, the first time they are inoculated and **b)** pregnant women who are in their second and third trimesters during the "influenza season" be so vaccinated.[16]

In 2006, the CDC[17] further increased the mercury-poisoning risk by broadening the influenza-inoculation age range to include children 6-months of age to 59-months of age and removed the "second and third trimesters" restriction[16] for pregnant women.

---

[13] Special Counsel Scott Bloch's letter to Congress addressed to: "The Honorable Judd Gregg, United States Senate, Chairman, Committee on Health, Education, Labor and Pensions, 428 Dirksen Senate Office Building, Washington, D.C. 20510-6300 and The Honorable Joe Barton, U.S. House of Representatives, Chairman, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515" [OSC File Nos.: DI-04-1399, et al.].

[14] Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). ***MMWR*** 2002 Apr 12; **51**(RR03):1-31 (with underlining added for emphasis): "Although no evidence of harm caused by low levels of thimerosal in vaccines has been reported, in 1999, the U.S. Public Health Service and other organizations recommended that efforts be made to reduce the thimerosal content in vaccines to decrease total mercury exposure, chiefly among infants and pregnant woman (**45**,**46**). … [45.] CDC. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. MMWR 1999;48:996--8. [46.] Stratton K, Gable A, McCormick MC, eds. Immunization safety review: thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC: National Academy Press, 2001.

[15] *ibid*., with underlining added for emphasis, "The 2002 recommendations include five principal changes or updates, as follows: … 3. Because young, otherwise healthy children are at increased risk for influenza-related hospitalization, influenza vaccination of healthy children aged 6–23 months is encouraged when feasible. …"

[16] **Who Should Get the Influenza (Flu) Vaccine: Interim Recommendations, December 2003**. December 16, 2003, as accessed through the CDC "Preventing the Flu" webpage site: "**Who Should Be Vaccinated With the Flu Shot This Season** … • Emphasis should be placed on targeting trivalent inactivated vaccine (flu shot) to persons at high risk for complications from influenza including: all children aged 6-23 months, adults aged > 65 years, pregnant women in their second or third trimester during influenza season, and persons aged > 2 years with underlying chronic conditions. • All children at high risk of complications from influenza, including those aged 6-23 months, who present for vaccination should be vaccinated with a first or second dose, depending on vaccination status. Doses should not be held in reserve to ensure that two doses will be available."

[17] http://www.fda.gov/fdac/features/2006/506_influenza.html, "**Who should get vaccinated?** Vaccine is available to anyone who wants to reduce his or her chances of getting influenza, with a few exceptions, but the CDC strongly recommends it for the following groups of people:
- All children 6 months to 59 months of age—a new recommendation for this influenza season
- Women who will be pregnant during the influenza season …"

doi: 10.1588/medver.2007.04.00145

In addition, we note that the FDA has just licensed another Thimerosal-preserved inactivated-influenza vaccine, FluLaval®, produced by the Canadian firm ID Biomedical Corporation, a subsidiary of GalxoSmithKline, which will apparently add 15 million more Thimerosal-preserved doses of inactivated-influenza vaccine.

Thus, contrary to either "goal," the federal government has, since 2002:

- Increased the risk of fetuses and infants being exposed to Thimerosal-preserved vaccines while still permitting preservative levels in other vaccines and drugs that may be given to infants and pregnant women
- Allowed other "reduced Thimerosal" and "trace" Thimerosal vaccines to also be administered to children, pregnant women, and nursing mothers, and
- Licensed a new Thimerosal-preserved inactivated-influenza vaccine.

Based on these facts, the government has *knowingly* failed to honor the "eliminate from, or reduce Thimerosal in all vaccines" goal it now claims to have as well as ignored its original 1999 commitment to remove Thimerosal from all childhood vaccines.

"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."

While your responses here attempt to present the facts in a light that focuses on the vaccines from which Thimerosal has been reduced or removed, your admission that the government has permitted the Thimerosal-preserved inactivated influenza to be added to the vaccination schedule for children "*children 6 to 59 months of age*" coupled with permitting Thimerosal-preserved vaccines to be given to pregnant women at any time in their pregnancy without any proof of safety to the fetus as well as to nursing mothers clearly indicates that the Secretary and the FDA are *knowingly*:

- Ignoring the statutes and laws limiting their discretion and,
- *Contrary to the implications of your statements here*, increasing the effective mercury-poisoning risk to the "child" by starting the mercury-poisoning before the child is born

so that the risk of mercury poisoning to infants receiving the maximum mercury exposure under the current vaccination schedule may, *in some cases*, exceed the previous risk for infants born to Rh-positive mothers who received all of the 1990s Thimerosal-preserved vaccines according to the schedule then in effect.

The specific dose, and *not* the dose, is important because, *for example*, a fetus weighing less than a half a kilogram may receive up to 40 micrograms of Thimerosal (about 20 micrograms of mercury) for a specific dose of greater than 40 micrograms of mercury per kilogram of body mass (40 parts-per-billion [ppb]).

In contrast, prior to recommending giving the Thimerosal-preserved inactivated-influenza vaccine to be given to pregnant women in 2003,[16] a typical 3 kg child born in 2003 who received even a 0.5-mL dose of an in-date Thimerosal-preserved hepatitis B vaccine, would have received a specific dose of only 8.3 micrograms of mercury per kg of body mass (8.3 ppb).
Thus, ignoring the toxicity differential between the fetus and the newborn, the fetus's specific dose would be about "5 times" (mathematically, "4.8 times") the dose received by our example newborn child.

Based on the preceding, it is clear to the **CoMeD** reviewers that the federal government, *by adding the Thimerosal-preserved inactivated-influenza vaccines to the recommended vaccination schedule for pregnant women without conducting the requisite reproductive toxicity studies to establish what the safe level is for the fetus or apparently even considering the increased risk of mercury-poisoning the fetus*, has, in spite of your glib rhetoric, *knowingly* increased the risk of mercury poisoning of children *in utero* rather than, *as their statements imply*, reducing the risk of poisoning children with mercury in the vaccines they directly and indirectly (*in utero*) receive.

Thus, we find that your rhetoric seems to be an blatant attempt to mislead the reader to think that the mercury-poisoning risk has been reduced by focusing on childhood vaccines from which Thimerosal has been removed or its level reduced without mentioning the increased mercury-poisoning of the children *in utero* when the children's mothers are inoculated with a Thimerosal-preserved vaccine when these mothers are pregnant.

doi: 10.1588/medver.2007.04.00145

"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's) Fluarix contains less than 1.25µg/mercury/dose and is approved for individuals 18 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."

We accept that the projected numbers of the various vaccines you discuss will be as you have stated.

However, since the current established limit for lethal toxicity (apoptosis) of Thimerosal to human neurons is < 0.001 µg of Thimerosal (< 0.0005 µg of mercury) per mL of growing neuron mesh (<0.0005 ppm mercury),[18] we find that the "reduced Thimerosal" and the "trace" Thimerosal vaccine doses will, if administered, deliver "< 2.0 µg to < 2.5 µg of mercury (< 4.0 to < 5 µg of Thimerosal) to 7-month old children given two doses of vaccine.

If nothing else, we note that injecting these "reduced Thimerosal" and the "trace" Thimerosal vaccines, the amount of mercury injected may exceed the established proven-human-neuron-poisoning level (< 0.0005-ppm mercury) at the injection site by more than a factor of 2,000 <u>even if</u> you allow a 2-fold dilution at the injection site!

Based on the preceding realities, we find that long-term toxicity studies would be needed to prove that even these "reduced Thimerosal" and the "trace" Thimerosal vaccine formulations are "sufficiently nontoxic" as **21 CFR 610.15(a)** indicates components, like preservatives, should be proven to be <u>before</u> they are used in a drug formulation.

Further, given the most generous estimates, there will be a maximum of 14 million doses of Thimerosal-preservative-free influenza vaccine for children < 59 months, according to the FDA through 2007.

Hence, again, based upon the population numbers reported in your response, there are 20 million infants and children in this age group, many of whom will need two doses each, then, *based on a 40% uptake rate*, there should be at more than 16 million Thimerosal-preservative-free doses.

However, because some of these doses will be administered to adults, including, for example, pregnant women, this will leave at least a million children in this age group who will be vaccinated with a Thimerosal-preserved vaccine.

In addition, the ACIP and the CDC are now recommending that an inactivated-influenza vaccine should be given to all women who are: **a)** pregnant or **b)** around children less than 6 months old, during the "influenza season" (an additional 4-million-plus doses).

Thus, based upon the need to vaccinate "*approximately 180 million Americans for whom the vaccine is recommended*," state laws and presuming that: **a)** most all of the 14 million doses of the "no" Thimerosal and "trace" Thimerosal vaccines will be administered to the affected children and **b)** the pregnant women and women with children under six months of age will receive either some of the "no" Thimerosal and "trace" Thimerosal vaccines, if they are under 18 years of age or, if 18 or older, GlaxoSmithKline's Fluarix®, we find that about 12 million "*children 6 to 59 months of age*" will either: **a)** *not* receive an influenza vaccine dose or **b)** be vaccinated with a Thimerosal-preserved vaccine.

Given the "*approximately 180 million Americans for whom the vaccine is recommended*" and subtracting the 24 million "*children 6 to 59 months of age*" and pregnant and other women discussed above, this leaves about 156 million Americans who will receive one of the remaining about 5 million doses of GlaxoSmithKline's "reduced Thimerosal"

[18] Parran *et al*. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. ***Tox Sci*** 2005; **86**(1): 130-140.

doi: 10.1588/medver.2007.04.00145

Fluarix, or the 3 million doses of MedImmune's Flumist® (live-virus), or about 90 million Thimerosal-preserved inactivated-influenza vaccine doses for a total of 98 million doses.

Presuming an average 50% uptake, about 73 million Americans will be competing for the remaining about 5 million doses of Fluarix; or, if they take the Thimerosal-free Flumist, risking becoming flu spreaders if they do *not* rigorously quarantine themselves from all others who have *not* been vaccinated with FluMist or, worse, risking being the progenitor for the next pandemic human influenza; or settling for being mercury-poisoned to possibly some significant degree if they chose to be vaccinated with one of the plentiful now 90 million (with the recent approval of FluLaval) doses of Thimerosal-preserved vaccines (Sanofi's Fluzone, Novartis' Fluviron, and, now, GlaxoSmithKline's subsidiary's FluLaval).

Since the government now projects 115 million total doses, it should be obvious that, given previous uptakes of no more than 75 million does, there will be more than enough influenza vaccine doses but there will be shortages of the "no Thimerosal" and "trace Thimerosal" vaccine doses.

Considering that the Public Health Service (PHS), American Academy of Pediatrics (AAP) and the manufacturers agreed to remove Thimerosal from all childhood vaccines in July 1999,[19] and as of 2007 (more than 7 years latter), a large portion of American children who are recommended to receive influenza vaccine and choose to be inoculated will still be forced to take a "Thimerosal Preserved" inactivated-influenza vaccine as well as, in some cases, some other "Thimerosal Preserved" vaccines in at least some formulations (*i.e.* tetanus-diphtheria toxoid, Japanese Encephalitis, tetanus-toxoid, meningococcal meningitis), the FDA's policy can hardly be called a great success.

Further, we find all of the preceding realities especially troubling because, as early as 1992, other developed western nations have been able to stop using Thimerosal-containing vaccines.

In addition, we find that the government's actions incomprehensible for influenza because, *based on the government's own statistics*, history has shown us that the inactivated-influenza vaccines are *not* effective[20, 21].

"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."

We find that your statement "*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*" is, ***at best***, misleading.

Factually*, until the late-1990s*, a Rh-negative pregnant woman receiving one generic Thimerosal-preserved Rho(D) product injections could add up to 50 micrograms of mercury for a total dose of 237.5 micrograms of mercury from conception until 6 months after birth.

Factually, *beginning in the late 1990s and with increasing urgency in the early 2000s*, pregnant women began to be advised to get flu shot when the only available shots were Thimerosal-preserved until the 2001-2002 flu season so that these children could have received a maximum dose of about 212.5 micrograms of Thimerosal – significantly more than your "*maximum cumulative exposure to mercury via routine childhood vaccinations during the first 6 months of life was 187.5 micrograms*".

Moreover, we note that, based on specific toxicity and actual experience,[22] the mercury-poisoning effects caused by the pre-natal 25- to 50- µg dose of Thimerosal are obviously much more severe than the effects for the same dose given after birth.

---

19 Notice to Readers: Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the Public Health Service. ***MMWR*** July 09, 1999; **48**(26): 563-565, with underlining added for emphasis, "Nevertheless, 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 removed as soon as possible."

20 Geier DA, King PG, Geier MR. Influenza Vaccine: Review of effectiveness of the U.S. immunization program, and policy considerations. ***J Am Phys Surg*** 2006; **11**(3): 69-74 and the supporting studies referenced therein.

21 Based in the preceding finding, we now also assert that the FDA should revoke the licensing of all influenza vaccines for those groups where post-approval in-use studies have failed to demonstrate effectiveness.

22 Ayoub DM, Yazbak FE. Influenza vaccination during pregnancy: A critical assessment of the recommendations of the Advisory Committee on Immunization Practices (ACIP). ***J Am Phys Surg*** 2006; **11**(1): 41-47.

doi: 10.1588/medver.2007.04.00145

"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."

We again find that your statement "*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*" is, at best, misleading.

Again, you improperly ignore both the administration of Thimerosal-preserved influenza vaccines to pregnant women as well as the fact that the government did *not* mandate the recall of all in-date doses of the existing Thimerosal-preserved vaccines.

Thus, *contrary to your assertion*, until 2005, the maximum dose of mercury an American child could receive from Thimerosal-preserved vaccines remained at not less than 237.5 µg of mercury.

Factually, the minimum "*cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life*" and *not* the "*maximum*" as you assert.

Obviously, as the "*thimerosal-preservative-free formulations of DTaP, hepatitis B, and Hib*," approved during the early 2000s began to displace their Thimerosal-preserved counterparts, the percentage of infants receiving the maximum mercury dose would have declined along with the incidence rates for adverse mercury-poisoning-related effects, if any.[23]

Since a drop in mercury-poisoning-related disorders was observed as the maximum level of Thimerosal dropped, we find that this drop has confirmed the reality that those disorders are tied to the mercury-poisoning effects of Thimerosal.

"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."

First, we find that the administration of influenza vaccines to children 6-months to 23-months, when feasible, was first recommended by the ACIP in 2002.[15]

Then, in December of 2003, the CDC[16] added the influenza vaccine to the "*the recommended vaccines*" for children 6-months to 23-months, recommended two doses for these children the first time they were vaccinated, and also added pregnant women in their second and third trimesters to the recommended schedule – not as you stated, "… *the addition in 2004 of influenza vaccine to the recommended vaccines*."

Thus, the recommendation to vaccinate children 6- to 23-months of age was first made in April 2002 – two years before your "in 2004" date.

In addition, since vaccine effectiveness studies have found that the influenza vaccine is no more effective than a placebo for children 2 years of age and under,[24] it appears to the **CoMeD** reviewers that the 2002, 2003, and 2006 recommendations are deliberate attempts by the government to replace some of the mercury removed from the other previously Thimerosal-preserved vaccine formulations with mercury from the Thimerosal-preserved influenza vaccines.

Moreover, we again find that your statement, "*This would result in a maximum exposure of 28 micrograms during the first 7 months of life via routine childhood vaccinations*," knowingly ignores the mercury-dose contribution from dosing these children *in utero*[16, 17]

Based on your statements, we find that it is clear that not only have you failed to evaluate the potential *in utero* mercury exposure contribution to the mercury-poisoning of children given "Thimerosal Preserved" influenza vaccines but you have also failed to accurately reflect the government's recommendations timeline for the dosing children 6–23

---

23 Factually, research studies into the changes in the incidence rates for autism and other neurodevelopmental disorders that are based on symptoms that mercury poisoning is known to elicit found that there was a decline in these during the early 2000s (**see**, for example, Geier DA, Geier MR. A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. ***Neuro Endocrinol Lett***. 2006 Aug 30; **27**(4); in press – **see** footnote 57).

24 Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Di Pietrantonj C. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. ***Lancet*** 2005; **365**: 773-780.

doi: 10.1588/medver.2007.04.00145

months of age and pregnant women or, worse, to address the disconnect between the government's 1999 recognition of the importance of reducing the maximum Thimerosal exposure in infants and pregnant women[15] and their actions from 2002 to date that have increased the maximum Thimerosal exposure from its pre-2002 minimum levels with, *in the case of pregnant women*, no apparent regard for increased specific toxicity to the fetus that inoculating a pregnant women with a "Thimerosal Preserved" influenza vaccine can cause.

Further, we note that your values fail to take into account that all pregnant women are recommended to receive an influenza vaccine (containing 25 micrograms mercury when they are inoculated with a Thimerosal-preserved vaccine).

In addition, for children turning 6-months in the 2006–2007 influenza season, their 6- and 7- month's inoculations will add 25 more micrograms of mercury.

Then, these children will receive an additional 12.5-microgram of mercury when they are between: **a)** "1" and "2," and **b)** "2" and "3" for 25 micrograms more mercury.

Next, between age "3" and age "5," they will receive 50 micrograms more mercury – for a total dose of up to 125 micrograms of mercury, provided the 2006–2007 (current) schedule remains unchanged, their healthcare provider adheres to the current schedule, and the children receive all Thimerosal-preserved vaccines.

In addition, they may continue to get additional 25-microgram doses annually if the government were to increase the cutoff age.

Thus, under the present recommended schedule, it is possible for a child to receive up to 125 micrograms mercury from Thimerosal-containing influenza vaccines (*i.e.* 25 micrograms mercury prenatally and 100 micrograms mercury postnatally) in comparison to a previous total of 237.5 micrograms of mercury during the same period of life under the 1999 vaccine schedule.

Thus, the present recommended schedule potentially can result in the children getting more than 50% of the total mercury dose that the 1999 schedule, with a significant prenatal vaccine-mercury exposure that was absent in 1999.

Finally, none of the above calculations take into account that mothers with young children are supposed to get an influenza immunization as well, and, *when they are breast-feeding their infant when they get the shot*, they will also transmit some of the vaccine-mercury with which they are injected to the infant through their breast milk.

"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.)"

First, we note that it appears that you have inappropriately used the EPA's estimated no-effect level (NOEL) for chronic daily ingestion of "methyl mercury" compounds in a fish matrix – 0.1 µg of mercury/per kilogram of body mass/day.

We find that using this ingestion NOEL is *fundamentally* inappropriate because:

1. Vaccines are injected in basically an isotonic saline matrix – *not* ingested in a fish matrix, and
2. The vaccine doses are bolus exposures – *not* chronic low-level exposures.[25]

Second, as the **CoMeD** reviewers have noted, the maximum Thimerosal-derived mercury dose at seven months is closer to 53 micrograms of mercury than it is to your stated "*28 micrograms*" because you recommend women who are pregnant during the "influenza season" ("October to March" in the U.S) should be inoculated with an inactivated-influenza vaccine.

Third, we note that your approach inappropriately presumes that there are no other sources of periodic or chronic mercury exposure in the infant.

---

[25] The medical "drug" analogy to your approach to judging risk would be claiming that taking one diuretic pill a day for 180 days would have the same outcome as taking 18 pills in one day every 10 days or 30 pills in one day once a month. Such approaches ignore the reality that the poisonous side effects of a toxic compound are strongly dependent upon its peak concentration. This is the case because the recipient's "detoxification" capacity is finite. On a more mundane level, your approach essentially equates drinking 1 shot (oz; 28.3 mL) of an intoxicating liquor (e.g., 80-proof whiskey) every day for 180 days to drinking 60 shots (60 oz; 1.7 L) of that liquor in one day every 60 days. Obviously, even you recognize that the outcomes in these two examples will be drastically different just as they are for periodically inoculating a baby with a dose of a Thimerosal-preserved vaccine

doi: 10.1588/medver.2007.04.00145

Since primate studies in baby monkeys[26] have established:

1. The uptake, transport, metabolism and excretion of the injected Thimerosal varied by more than an order of magnitude in the 17 baby monkeys in the Thimerosal-treatment arm even though the dosage was adjusted for the differences in each subject's body weight,
2. On average, a significant part of the Thimerosal injected ended up in the monkeys' brains as "inorganic mercury" where its half-life was estimated to be > 120 days[27],
3. On average, the half-life for the "organic mercury" (where the organic mercury level is determined by measuring the inorganic mercury level and the total mercury level and subtracting the inorganic from the total) in the brain was about 24 days,

the more appropriate approach to estimating incremental mercury toxicity risk is to divide the amount of Thimerosal injected when a large bolus is injected by twice the EPA's 0.1 µg/kg/day value and sum the values found to estimate the maximum relative risk of mercury poisoning in those individuals who do *not* efficiently detoxify themselves from mercury (those individuals who, for example, have APO-E2, and innately low glutathione levels).

Using that approach and, for example, a fetus weight of 0.5 kg, a 6-months' weight of 3.6 kg, a 7-months' weight of 4.0 kg, an 18-months weight of 10 kg, a 30-months' weight of 18 kg, a 42-months' weight of 24 kg, and a 54-months' weight of 30 kg, the corresponding maximum mercury-poisoning "risk" factors are about:

1. 20.0 µg[28]/0.5 kg x 10 kg/µg = 400 for the *in utero* exposure,
2. 12.5 µg/3.6 kg x10 kg/µg = 34.7 for the 6-months' exposure,
3. 12.5 µg/4.0 kg x 10 kg/ µg = 31.3 for 7-months' exposure,
4. 12.5 µg /10 kg x 10 kg/ µg = 12.5 for the 18-months' exposure,
5. 12.5 µg /18 kg x 10 kg/µg = 6.9 for the 30-months' exposure,
6. 25.0 µg /24 kg x 10 kg/µg = 10.4 for the 42-months' exposure, and
7. 25.0 µg /30 kg x 10 kg/µg = 8.3 for the 54-months' exposure,

for a total of 120 µg of vaccine derived mercury from the bolus inoculations with a total maximum relative risk of about 500. [**Note:** If the mother is *not* vaccinated during pregnancy, the maximum risk in this example calculation would drop to about 100 – roughly indicating how much more poisonous the mercury the *in utero* child acquires is compared to the estimated maximum relative risks for the other Thimerosal-preserved influenza vaccine inoculations for children up to 59 months of age.]

Based on this bolus-dose approach, the maximum amount of influenza-vaccine-derived mercury dosed maximally exceeds the EPA's toxic level by greater than a factor of 500.

Hopefully, the preceding hypothetical example will help the reader and the FDA to understand the approximate maximum mercury poisoning risk relative to the 0.1 µg/kg/day EPA NOEL estimate (developed by the EPA for ingested "methyl mercury" species in fish) that the Thimerosal-preserved influenza vaccines represent to human children.

"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."

We agree with you that: **a)** your concern has been focused on childhood vaccines and **b)** the **CoMeD** petition, as it should, "*extends to vaccines indicated for all ages*."

However, since the injected mercury in vaccines and other drugs tends to bioaccumulate in the brain, kidneys, heart and other organisms and the degree of accumulation over the "normal" levels is highly variable across both organs

---

[26] Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal. ***Environ Health Perspect***. 2005 April 21; **113**(4). 36-page draft "pdf" file. [Final article at doi: 10.1289/ehp.7712 (available online at http://dx.doi.org).]

[27] Based on human autopsy studies on accident victims, the half-life ("half-time") for "inorganic mercury" in the brain was found to be 22 years. [Sugita M. The biological half-time of heavy metals. The existence of a third ''slowest'' component. ***Int Arch Occup Environ Health*** 1978; **41**(1):25–40.]

[28] Though the fetus has been shown to be a "sink" that accumulates mercury, studies in rabbits indicate that only about 80% of the does accumulates in the developing fetus.

and individuals, we *cannot* agree that the standard recommendations for adults necessarily lead to "*correspondingly lower mercury exposure from vaccines*."

First, because of the two-plus-decades-long half-life for accumulated tissue bound "inorganic mercury" in various organs and the initial dosing, each person entering the "adult" population under the previous recommended vaccination programs starts out with maximum organic-derived mercury exposure of up to about 240 µg and those under the current program will get up to about 125 µg from the preserved influenza vaccines received up to 59-months of age and then receive up to two 25-µg doses of organic-derived mercury from the multi-dose Menomune® vaccine (50 µg of mercury) plus one to three 25-µg doses of organic-derived mercury from the TT vaccine (25- to 75- µg of organic-derived mercury) and, when any at-risk group continues to get an annual preserved "flu" vaccine, up to twelve, 25-µg doses of influenza-derived mercury (300 µg) for a total of up to 550 µg (665 µg, if vaccinated under the pre-2000 program) of vaccine-derived mercury.

Then, when this hypothetical person continues getting an annual Thimerosal-preserved flu shot and, every 10 years, a TT booster vaccine, that person will, by the time they reach 68, have received a maximum additional 50 times 25 µg of mercury from Thimerosal in Thimerosal-preserved influenza vaccine and 125 µg of mercury from the Thimerosal-preserved TT vaccine for a total of 1,925 µg (1.9 mg) of vaccine-derived mercury (or, under the previous program, up to about 2 mg of mercury).

Presuming our hypothetical 68-year-old weighs 80 kg, the maximum mercury-poisoning risk factor will then be 1,925 µg of Hg/80 kg x 10 kg/µg = 240.6 times the EPA's estimated NOEL toxicity risk level (or 250 times NOEL risk in "previous" case).

Thus, the maximum total vaccine-mercury dose will be about 15 times the level in the child at 59 months and the risk factor will be about 200 times the EPA's NOEL for ingested methyl mercury in fish.

Since, *as we have shown*[20], the influenza vaccines are ineffective, we again note that making influenza vaccination an optional practice and *not* vaccinating pregnant women would lower the mercury poisoning maximum early childhood risk factor to about 100 and the imputed maximum risk factor for the elderly adult to "< 25."

"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."

Since the vaccine manufacturers have been able to remove Thimerosal for all of these new vaccines and some manufacturers have been able to totally remove Thimerosal from their existing Thimerosal-preserved and/or "reduced Thimerosal" vaccines, we see no justification in continuing to license any Thimerosal-preserved vaccine, especially since the Thimerosal-preserved influenza vaccines have been shown to be ineffective.

Further, unless and until, the appropriate safety studies prove these preserved vaccines are "sufficiently nontoxic" as per **21 CFR § 10.15(a)**, these Thimerosal-preserved vaccines are clearly adulterated drugs under **21 U.S.C. 351(a)(2)(B)**, leaving the FDA and the Secretary in the position of, *at a minimum*, condoning the knowing violation of the law by the firms manufacturing these vaccines and, thereby, placing themselves above the law of the land.

In addition, we find that your recent (5 October 2006) licensing of another Thimerosal-preserved influenza vaccine without obtaining the requisite proofs of safety required under **21 CFR § 610.15(a)** after being clearly shown that such an action is a clear violation of the preceding law and against the clear mandates set forth in **42 U.S.C. Sec. 300aa-27(a)(2)** has plainly signaled your blatant and knowing disregard for the "law of the land" as established by the Supreme Court in 1988 as well as your apparent belief that you and, through you, vaccine manufacturers are above the laws of the United States of America.

As such, it seems to the **CoMeD** reviewers that your collusive actions with those vaccine manufacturers who have, *since 1973*, *knowingly* held themselves above the law, fall within the umbrella established by the criminal RICO (Racketeering, Influencing, and Corrupt Organizations) statutes as set forth in **18 U.S.C.A Sec 1961 *et seq.*** and, in

doi: 10.1588/medver.2007.04.00145

light of the recent licensing of another Thimerosal-preserved influenza vaccine, we are compelled to request the court to initiate and pursue such actions.

"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."

Given the ineffectiveness of the worst offender, the Thimerosal-preserved influenza vaccines; your recent knowing actions; and the clear requirements of the law, the **CoMeD** reviewers finds your attempts to justify your knowing failure to act within the law and as the statutes require you to act unconvincing.

In addition, we find no evidence of the "*serious danger*" of which you speak and you have submitted none.

Further, we note that Aventis, now Sanofi-Aventis representatives, the principal producers of the remaining Thimerosal-preserved vaccines and many of the "trace Thimerosal" vaccines, have stated that they would be able to provide sufficient "no Thimerosal" vaccine if the federal government were to mandate that such must be provided.

Additionally, *contrary to your position*, we find that all that needs to be produced is sufficient doses for all those who seek such vaccines and *not*, as you assert, "*all those who should be immunized*."

For all of these preceding reasons, we find your attempts to justify your failures to operate within the applicable laws and statutes to be both unjustified and unjustifiable.

We therefore again urge you to turn from your violative ways and conform to the clear legal requirements with which the Supreme Court has plainly ruled, *in a unanimous decision*, you are required to conform.

"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."

Since you have failed to address the laws and statutes cited by **CoMeD** and, *in most cases*, have failed to provide any scientific evidence to overcome the peer-reviewed published studies and their findings, the **CoMeD** reviewers are compelled to reject your rhetoric here.

Further, we note that your remarks here concerning our supposed "*contention that those vaccines are unsafe*" clearly ignores the fact that one of our actual contentions was and is a contention that you have *not* even addressed, namely the contention that these Thimerosal-preserved vaccines have *not*, *as required by law*, been proven to be safe under the clear minimum requirement for the safety of a preservative ("sufficiently nontoxic") as set forth in **21 CFR § 610.15(a)**.

In addition, we again note that you have failed to mention, much less address, our other main contention, namely that, under **42 U.S.C. 300aa-27(a)(2)**, you both are required to do all you can to reduce adverse reactions in childhood vaccines and, *as your failure to remove all Thimerosal from vaccines starting in 1987, when that statute became effective, and continuing to today clearly establish*, you both have knowingly ignored and flouted this statutory requirement for almost two decades after the U.S. Supreme Court clearly ruled you did *not* have the "discretion" to ignore any such statute.

Therefore, since you have neither addressed our underlying concerns nor presented any substantive proofs to support your claims concerning the petition-supportive evidence we have submitted, we must reject your contentions here.

"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 Rho(D) immune globulin that contains thimerosal that is still in-date."

doi: 10.1588/medver.2007.04.00145

We applaud you for getting the affected manufacturers of these "*plasma derivative products*" to comply with the spirit of **21 CFR § 610.15(a)** – to ensure that such are "sufficiently nontoxic" – and note that they had no problem removing their Thimerosal-preserved products from the market and switching to unit-dose/single-dose packaging precluding the need to use any preservative because, *by their very nature*, all preservative systems that are effective in killing microbial organisms are somewhat toxic to humans.

Since this is the case for "*plasma derivative products*," we again wonder why you have *not* taken similar action to compel the manufacturers of Thimerosal-containing childhood vaccines containing a level of Thimerosal that has been proven to cause adverse reactions, including mercury poisoning, to switch to "no Thimerosal" formulations to reduce the adverse reactions such are known to cause under the clear statutory mandate for you to do so set forth in **42 U.S.C. Sec. 300aa-279a)(2)**.

"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."

While we find that your statements represent your view of reality, we note that **Title 42 – THE PUBLIC HEALTH AND WELFARE** – **of the United States Code** specifically allows the Public Health Service (PHS) to manufacture any licensed biological product should there be any need to do so

This authority is granted under **42 U.S.C. Sec. 263,** which states:

"Sec. 263. Preparation of biological products by Service

(a) The Service may prepare for its own use any product described in section 262 of this title and any product necessary to carrying out any of the purposes of section 241 of this title.

(b) The Service may prepare any product described in section 262 of this title for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section."

Thus, we recommend that the Secretary instruct the PHS to develop and manufacture mercury-free formulations for these important biological products until such time as the commercial manufacturers begin manufacturing these "no mercury" biological products.

We make this recommendation because, though you failed to mention it in your response:

- These four plasma-derived products not only contain high-level preservative concentrations of Thimerosal (on the order of 80 to 120 µg of Thimerosal [40 to 60 µg of mercury]/mL) but also prescribe giving the patient multiple-milliliter doses, which results in the recipient of these products getting significantly larger bolus doses of mercury than other Thimerosal-preserved drug products.
- Additionally, unlike other Thimerosal-containing drug products, which are administered intramuscularly, subcutaneously or topically, these products are can not only be administered intramuscularly but can also be administered intravenously (*i.e.*, infused directly into the recipient's blood stream).

For example, Black-widow-spider antivenin's dosing instructions recommend starting with the intramuscular or intravenous administration of 2.5 mL to the patient.

Thus, a patient may receive 100 to 150 micrograms of mercury from a single recommended administration of this product.

As a result, an adult weighing 50 Kg would initially receive 2 to 3 micrograms of mercury / kg and, *since there is no provision for weight-based dosing*, a young child weighing 5 kg would get 20 to 30 micrograms mercury / kg – essentially doses that are, respectively, 5 and 10 times higher than the bolus dose provided by a Thimerosal-preserved influenza vaccine.

doi: 10.1588/medver.2007.04.00145

Based on all the preceding, your contention that "*the few snake and spider antivenoms that contain thimerosal create minimal exposure*" is at odds with the facts from the patient's point of view and can only be considered valid if your "*minimal exposure*" assertion is taken to be addressing the number of people treated each year.

Therefore, given: **a)** the increased mercury-poisoning risk the antivenom products present, **b)** the manufacturers' apparent exiting the market, and **c)** the important need for these life-saving antivenom products, we recommend that the "lack of proof of safety" issue should be dealt with by having the Secretary direct the Public Health Service (PHS) to take over in this area, and develop, license and provide preservative-free doses for each of these antivenoms.

"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 be 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."

Since, as your "*FDA believes*" rhetoric clearly indicates, the FDA lacks the requisite toxicological studies required to prove the implicit "sufficiently nontoxic" requirement for the safety of these products and there is no prohibition on giving these products to young children and pregnant women, these drug products should only be allowed to continued to be used if there manufacturer proves that they are "sufficiently nontoxic."

Moreover, since, in some cases, these products may be and are prescribed for chronic daily use over some period of time, we find that proof that such are "sufficiently nontoxic" to the recipient is more important than in the case of vaccines because they are given fairly infrequently.

Based on the preceding realities, we must reject your belief-based contention "*that the mercury exposure from such products is minimal*."

Thus, we again call on you to prove that these preserved drug products are "sufficiently nontoxic" under the clear CGMP minimums set forth in **21 U.S.C. Sec. 351(a)(2)(B)**.

"C. The Few Products that Still Contain Thimerosal are Safe

1. *To be safe means 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))."

Provided:

- All the short-term and long-term harmful effects are proven, *by the appropriate scientifically sound toxicological studies*, to be minimal, and
- The safety standard minimums established for a given component are met,

then we:

- Have no problem with your using the "safety" definition set forth in **21 CFR § 600.3(p),** but
- Note that nowhere in this definition do we find the phraseology you have chosen to use: based on a comparison of "*the benefit of the … product as compared to the risk of the side effects*."

Since all vaccines, except the rabies vaccine, are intended to be given to healthy persons, then, under **21 CFR § 600.3(p)**, vaccines should be proven safer than those other categories of drugs that are intended to be given to people that are less than healthy, those having a disease or illness.

Thus, *in plain English*, this definition does *not* address, or permit, your "*(t)o be safe means that the benefits outweigh the risks*," interpretation of a definition which states, "The word safety means 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," and clearly requires, *for vaccines*, weighing the "relative freedom from harmful effects" against the "condition of the recipient at that time" without regard

doi: 10.1588/medver.2007.04.00145

to the unknown benefits since, some who are inoculated will get no protection and, *unless exposed to the disease*, the protection provided for most vaccines is only theoretical.

Thus, we must reject your "risk *versus* benefits" assertion as it is clearly at odds with the definition provided here.

"If the benefit of the vaccine or other pharmaceutical product outweighs the risk of the side effects, then FDA finds the product safe."

First, *if this is what you are doing*, we find that your actions are outside the law based on the definition upon which you claim to rely – namely, **21 CFR § 600.3(p).**

Second, to the extent this statement implicitly asserts that you are the sole arbiter of both the "*benefit*" and the "*risk of the side effects*" and that the your "discretion" is *not* limited by policies, laws, and statutes that establish clear safety requirement minimums, we find that, *under Berkovitz*,[1] your position is at odds with the unanimous findings of the US Supreme Court.

Third, *as we have repeatedly asserted and you have repeatedly failed to address*, the extent of harm of the "*side effects*" must be proven by suitable rigorous toxicological studies, which, *as you have admitted and Congress has reported*,[7] have *not* been done for Thimerosal (49.55% mercury by weight) or the other mercury-containing compounds used as process sterilants or preservatives in the manufacture of some vaccines and other drug products – thus, your silence clearly establishes that you have no rigorous proof that plainly establishes the side effects' harm.

Lacking proof of the level of harm also means that you have no "proof of safety."

Lacking proof of safety, you *cannot* make any valid assessment of "safety" under **21 CFR § 600.3(p).**

Fourth, *given Berkovitz*[1], **21 CFR § 610.15(a)**, **21 CFR Part 211**, **21 U.S.C. Sec. 351(a)(2)(B)**, and **42 U.S.C. 300aa-27(a)(2)**, *at a minimum*, you have been explicitly required, *since 1973*, to require the manufacturer of any preserved biological drug product to prove that "the preservative used" is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" and, *implicitly*, under **21 U.S.C. Sec. 351(a)(2)(B)**, to prove this level of safety for the preservative systems in all preserved drug products, and, *to date*, the manufacturers of preserved biological drug products have failed to prove that Thimerosal or other mercury-containing compound used as a preservative in their drug products have meet this clear "safety" requirement *minimum*.

Fifth, *given Berkovitz*[1] *and* ***42 U.S.C. 300aa-27. Mandate for safer childhood vaccines***, you have been mandated, *since 1987*, under **42 U.S.C. 300aa-27 (a)(2)**, to do all you can within the authorities of the Secretary of HHS "to reduce the risks of adverse reactions to vaccines."

Since all Thimerosal-containing vaccines, even, *in those who are allergic to Thimerosal*, the "trace Thimerosal" ones can and do cause adverse reactions and, *in many cases*, serious adverse reactions including anaphylactic shock and death, you should have been removing Thimerosal-containing childhood vaccines from the market as fast as you could from January 1988 onward and, *recognizing that this requirement implicitly applies to all drugs because adverse reaction reduction safens all drugs*, from all other vaccines and drugs.

However, your actions, including recently licensing another Thimerosal-preserved influenza vaccine and failing to pressure all vaccine manufacturers to reformulate all their childhood (and other vaccines) without any Thimerosal clearly indicate that you have knowingly failed to comply with this statutory mandate.

Based on all of the preceding, at a minimum, you need to:

- Correct your violative actions with respect to **42 U.S.C. 300aa-27(a)(2)**,
- Compel the manufacturers to comply with the law and prove what the safe level is for Thimerosal – the level at which Thimerosal is "sufficiently nontoxic" at the dose given to all those who are administered a vaccine, or other biological product, formulation containing it that these inoculees have no short-term or long-term adverse reactions or evidence of mercury poisoning as explicitly required for biological products in **21 CFR § 610.15(a)**,
- Enforce the "adulterated drug" sanctions for all preserved vaccine lots where the manufacturers have failed to comply with **21 CFR § 610.15(a)**,

before you can legally assess the safety of any "mercury-preserved" mercury-compound containing biological product under **21 CFR § 600.3(p)**.

doi: 10.1588/medver.2007.04.00145

In addition, in the area of vaccines, you need to reassess the benefits claimed by proving that the in-use experience of each vaccine establishes that that vaccine is truly effective – since, as you will *hopefully* agree, under **21 CFR § 600.3(p)**, a vaccine that is *not* truly effective *cannot* be safe because it provides no assured benefit.

Since the in-use history of the inactivated-influenza vaccines has clearly established that they are ineffective,[20] it is clear that, under **21 CFR § 600.3(p)**, they are *not* safe and you should immediately stop the CDC's "recommended influenza vaccination programs," and recall and destroy all lots of the Thimerosal-preserved inactivated-influenza vaccines because they are *not* safe under **21 CFR § 600.3(p)** and they have *not* been proven safe to the extent required by **21 CFR § 610.15(a).**

"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."

Provided you:

- Operate within the limits on your discretion imposed by *Berkovitz*,[1]
- Fully comply with all statutes that govern your conduct (including, but *not* limited to, **42 U.S.C. 300aa-27** and **21 U.S.C. Sec. 351(a)(2)(B)**),
- Require the drug manufacturers to: **a)** comply with the clear mandated minimums set forth in **21 CFR § 610.15(a)**, **21 CFR Parts 210 and 211**, and any other binding regulations, and **b)** *in light of Vioxx*, fully disclose all studies and all reports of adverse effects within 15-days of their receipt, and
- Stop relying on the manufacturer's evaluation of the claimed benefit and conduct an independent assessment of the real benefits and their per-person-benefited costs,

we have no problem accepting your views here.

However, we are compelled to note that vaccines must be held to a higher standard of safety than all other drug categories because, *except for the rabies vaccine*, vaccines are given to healthy people for the purpose of protecting them from diseases that they do *not* currently have and, *if not exposed*, will *not* contract.

"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."

We *cannot* agree with you here because, as stated, your views fail to comply with *Berkovitz*.[1]
Based on *Berkovitz*,[1] you must first make sure, in order of precedence, that:

- All clear regulatory standard minimums (policies, regulations, and statutes) for a vaccine are met,
- You have scientifically sound and appropriate proof that clearly establishes: **a)** what all of the short-term and long-term risks are for the vaccine and **b)** what their incidence rates are,
- You have unbiased, scientifically sound, and complete estimate of the putative benefits and their probability of protection and the duration of that probable protection,

before you should begin to weigh the risk of any such drug against its benefits.

To date, *based on your actions and failures to act*, you have failed to meet all of these basis requirements for all Thimerosal-containing vaccines.

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

We must reject your assertions here because:

- You have *neither* presented *nor* referenced any body of scientifically sound, peer-reviewed and published "*evidence*" to support your "*the evidence favors*" assertion,
- Since **CoMeD**'s "*risks*" claims are supported by a body of scientifically sound, peer-reviewed and published "evidence" that **CoMeD** both quotes and references, **CoMeD**'s claims are statements of fact and *not*, as you state, "allegations,"
- You have failed to present or reference any body of scientifically sound, peer-reviewed and published "*evidence*" to support your generalization that "*the benefits are lifesaving and well-established* and
- The **CoMeD** reviewers have presented scientifically sound, peer-reviewed, published evidence that the influenza vaccines are ineffective,[20] which clearly rebuts the validity of your generalization.

doi: 10.1588/medver.2007.04.00145

"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."

Since you have failed to provide any evidence to support your assertion that "*Thimerosal has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines*," we *cannot* accept your assertion as being more than rhetoric.

In addition, you have *neither* responded to *nor* considered the evidence directly presented in the petition with regards to the lack of effectiveness of 0.01% Thimerosal as a preservative in vaccines.

The article by Stetler *et al*.,[29] which we chose to submit in the petition to show that Thimerosal is *not* an ideal preservative, is one authored by researchers from the CDC.

Among other things, their article, titled "Outbreaks of Group A Streptococcal Abscesses Following Diphtheria-Tetanus Toxoid-Pertussis Vaccination," stated:

- "At currently used concentrations thimerosal is not an ideal preservative."
- "The thimerosal preservative present in DTP vaccine requires substantial time to kill organisms and cannot be relied upon to prevent transmission of bacteria under conditions of practice when a vial is used over a short period."
- "Laboratory experiments in this investigation have shown up to 2 weeks' survival of at least one strain of group A Streptococcus in multidose DTP [Diphtheria-Tetanus-Pertussis] vials."
- "The manufacturer's preservative effectiveness tests" [at 0.01 % (100 micrograms of Thimerosal {50 micrograms of mercury} per milliliter)] "showed that at 4^{o}C, 4.5% of the challenge Streptococcus survived 14 days after inoculation into a multi-dose DTP vaccine vial."
- "Instead, the most important means of preventing abscesses secondary to DTP vaccination is to prevent contamination by careful attention to sterile technique."

These findings by CDC researchers clearly implicate the lack of effectiveness of Thimerosal and recommend that the only way to prevent bacterial contamination in vaccines is to proactively prevent the introduction of bacteria into vaccine vials (*e.g.*, by the use of pre-filled single-dose vials/syringes/injectors).

Additionally, because you have failed to accept the clear evidence provided by the study by Stetler *et al*.[29] that was reported in our citizen petition, we submit the following series of additional historical studies that clearly establish that Thimerosal is *not* fully effective as a preservative:

1. An anonymous 1943 ***JAMA*** publication that questioned the use of Thimerosal as a 'preservative,' concluded:
   " In a recent study of protein sulfhydryl groups Hellerman, Chinard and Deitz point out that organometallic compounds of the type R-Hg-X … form poorly dissociated protein mercaptides by combination of the organic mercurial with proteins and thiol groups. According to Fildes the formation of such mercaptides is the basis for the bacteriostatic action of mercury. Such sulfhydryl groups are present, however, not only in bacteria but in plasma and other proteins. Bacteriostatic action of such organomercuric compounds in the presence of serum is therefore largely prevented by competition of reactive groups on the serum proteins for the mercury. This presumably is the basis of the funding that the 'activity of a mercurial antiseptic in serum is reduced to 0.33-0.0007 percent of its activity in saline.' Ignoring these chemical facts can be responsible for very serious occurrences, such as the arrival in England of plasma 'preserved' with 1:10,000 Merthiolate containing viable micro-organisms…In our experience 1:10,000 Merthiolate has not been able to insure the sterility of stored liquid plasma. The contaminations reported in this paper in plasma-saline mixture containing 1:10,000 Merthiolate are sufficient to be an argument against its use. The material found to be contaminated when tested after its arrival in England is further evidence that 1:10,000 Merthiolate cannot be considered the ideal preservative…"[30]

[29] Stetler HC, Garbe PL, Dwyer DM, Richard R. Facklam RR, Orenstein WA, West GR, Dudley KJ, B. Bloch AB, Outbreaks of group A streptococcal abscesses following diphtheria tetanus toxoid-pertussis vaccination. ***Pediatrics*** 1985; **75**(2): 299-303.

[30] Anonymous. 1943. Mercurials as 'preservatives.' *J. Am. Med. Assoc.* 122:1253.

doi: 10.1588/medver.2007.04.00145

2. Morton *et al*. (1948),[31] under a grant from the Council on Pharmacy and Chemistry of the American Medical Association, published an article on the bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci. They reported:

   "…the label on a bottle of 'Solution Merthiolate, 1:1,000, Stainless' purchased as recently as June 1947 states that it is 'a stable, stainless, organic mercury compound of high germicidal value, particular in serum and other protein media.' It is not highly germicidal and especially does not possess high germicidal value in the presence of serum and other protein mediums. The loss of antibacterial activity of mercurials in the presence of serum proves their incompatibility with serum… The comparative in vitro studies on mercurochrome, metaphen and Merthiolate on embryonic tissue cells and bacterial cells by Salle and Lazarus cannot be ignored. These investigators found that metaphen, Merthiolate and mercurochrome were 12, 35 and 262 times respectively more toxic for embryonic tissue cells than for Staphylococcus aureus. Nye and Welch also found the same three mercurial compounds more toxic for leukocytes than for bacterial cells. Not only is there direct toxic action of the mercurial compounds on the cellular and humoral components of the animal body, but there is also the possibility of sensitization."

3. Engley (1950)[32] of the Biological Department, Chemical Corps, Camp Detrick published an evaluation of mercurial compounds as antiseptics. Engley judged mercurials to be inadequate as antiseptics:

   "Mercurial compounds have not enjoyed a peaceful career as antibacterial chemicals since their popularization as germicides over sixty years ago (Kock, 1891)…During the ensuing years, other workers, using various techniques, have also shown that the antibacterial activity of mercurials is only slowly bactericidal and mainly bacteriostatic. This bacteriostasis is even nullified by the presence of many types of sulfur-containing compounds, including sulfides (Geppert, 1889), (Hunt, 1937), thioglycollate (Marshall, Gunnison, and Luxen, 1941), body fluids such as plasma (Johnson and Meleney, 1942), and other organic matter (Greeen and Birkeland, 1944)."

   Furthermore, *and of even greater concern*, was Engley's conclusion that mercurials, such as Thimerosal, "…are ineffective in vivo and may be more toxic for tissue cells than bacterial cells, as shown in mice (Nungester and Kempf, 1942) (Saber, 1942) (Spaulding and Bondi, 1947), tissue culture (Salle and Catlin, 1947), and embryonic eggs (Witlin, 1942) (Green and Birkeland, 1944), and with leucocytes (Welch and Hunter, 1940)."

4. Subsequently, Engley (1956)[33] presented a paper to the 42nd midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago, Illinois. Engley overtly questioned the acceptance of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating:

   "The use of mercurials as preservatives in vaccines and antisera is of considerable interest. These chemicals are added to protect against the introduction of organisms in multi-use containers in particular. We have always wondered about their efficacy in that both vaccines and antisera contain reactive groups to tie up these compounds. In a series of continuing experiments over the past several years we have begun to evaluate various preservatives in serum and vaccines under conditions of use. Employing stock vaccines and serum with and without preservatives and stored at varying lengths of time a contaminating dose of representative sporeformer (Bacillus subtilis) in the spore stage gram-negative rod (E. coli) and gram-positive coccus (S. aureus) were added. While the mercurial preservatives had good activity on initial addition, after storage of three, six or more months decreasingly less to negligible residual activity appeared to be left, indicating that the chemical was tied up by the protein of the biological or otherwise inactivated. A check on a series of over one thousand bottles of various biologicals from clinics obtained after use revealed that up to five percent contained micro-organisms. This would suggest that once these biologicals are in the hands of users a problem still exists. Regarding preservatives, one of the real problems existing in hospitals and clinics is the need for good preservatives in the routine eye dilators and nasal preparations of the decongestant type. Routine checks of these indicate a high percentage of contaminated solutions. In one instance we had direct evidence of upper respiratory cross-infection from the use of a common nasal dropper preparation in a clinic."

   Engley then gave an evaluation of the relative toxicity of mercurials, such as Thimerosal, by stating:

   "The toxicity of chemicals used as drugs on or in the body has been of considerable interest since man first began exposing himself to various chemicals many years ago. Unfortunately there have not been good

---

31 Morton, H. E., North, L L., and Engley, F. B. 1948. The bacteriostatic and bactericidal actions of some mercurial compounds on Hemolytic streptococci: in vivo and in vitro studies. *J. Am. Med. Assoc.* 136:37-41.

32 Engley, F .B. 1950. Evaluation of mercurial compounds as antiseptics. *Ann. N. Y. Acad. Sci.* 53:197-206.

33 Engley, F. B. 1956. *Mercurials as Disinfectants: Evaluation of Mercurial Antimicrobic Action and Comparative Toxicity for Skin Tissue Cells*. Chicago, IL: 42nd Mid-Year Meeting of the Chemical Specialties Manufacturer's Association.

doi: 10.1588/medver.2007.04.00145

techniques for toxicity determinations of certain types of chemicals which might be really indicative of toxicity for humans...Graph 15 compares mercurial compounds and shows how they fit in with other compounds in toxicity...Mercurochrome appears to be the least toxic ranging down through Merthiolate...One point should be made here. Bichloride of mercury has always been pointed out as an extremely toxic mercurial and the organic mercurials were supposed to be much less toxic but according to these data we find bichloride right in the middle of the organic mercurials in regard to cell toxicity."

Finally, it should be noted, with respect to the toxicity experiments undertaken by Engley, that he determined Thimerosal was significantly toxic to human tissue-culture cells at a concentration of 10 parts-per-billion (ppb).

5. Hekkens *et al*. (1983)[34] undertook an evaluation of the effectiveness of some preservatives in inactivated human vaccines by application of the test described in the **United States Pharmacopoeia (USP) XIX**. These researchers described that five recommended strains as well as three strains isolated from vaccines were used as test strains. It was observed that vaccines preserved with Thimerosal did *not* fully meet the requirements for a vaccine preservative according to the criteria established by the **USP XIX**.

6. Lowe and Southern (1994)[35] evaluated the antimicrobial action of various preservatives for vaccines. They reported:

"'The preservative most commonly used is Thiomersal. Other preservatives are being evaluated because: (i) this material has become difficult to obtain; (ii) the use of mercury-containing compounds in medicinal products is considered potentially harmful; and (iii) it has been found that some vaccine components are unstable in the presence of this material.' In light of these facts, the researchers undertook a series of experiments comparing the antimicrobial activity of phenoxyethanol with Thimerosal in diphtheria, tetanus, and pertussis (adsorbed) vaccine. It was observed, "(b)oth chemicals were equally effective in inactivating challenge doses of Gram-negative and Gram-positive micro-organisms, as well as yeast."

Furthermore, the authors stated, "… low toxicity of phenoxyethanol in children has been reported…"

Hopefully, after reading these published historical reports, you and any reader will agree that Thimerosal is *not* effective "*in preventing bacterial and fungal contamination of vaccines*" and there are other less toxic compounds that are suitable for use as biological drug product preservatives

In addition, your "*Thimerosal has a long record … with no ill effects established other than hypersensitivity and minor local reactions at the site of injection*" is at odds with factual reality.

First, we note that, *by the FDA's own admission*, Thimerosal does have established adverse reactions.

In considering hypersensitivity, it is significant that, under worse-case scenarios, this type of adverse reaction can manifest as anaphylaxis and result in the death of the patient.

Second, no data is presented, as required by statute to prove that Thimerosal is "sufficiently nontoxic."

The only evidence purporting to bear on the safety of using Thimerosal as a preservative are reviews by the IOM[Let-3], [Let-4] and the CDC (Parker *et al*.) that you report, which conclude the evidence is *not* consistent with Thimerosal's causing autism but do *not* speak directly to its safety or the mercury poisoning it may cause.

In actually reviewing the cited studies, a significant number do provide peer-reviewed scientific epidemiological evidence showing a significant increased risk for neurodevelopmental disorders, including autism, following exposure to Thimerosal-containing vaccines.

"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]

The **CoMeD** reviewers are heartened to see that you have at least addressed one of our underlying concerns – that repeated injection with Thimerosal-containing vaccines leads to clinical levels of mercury poisoning because Thimerosal has been shown to bioaccumulate in mammals with worst-case half-lives for the end-stage metabolites of Thimerosal that have been reported to approach or exceed two decades.

---

34 Hekkens, F. E. An., Polak-Vogelzang, A. A., and Kreeftenberg, J. G. 1983. The antimicrobial effectiveness of some preservatives in inactivated human vaccines. ***J Biol Stand*** 1983; **9**:277-285.

35 Lowe I, Southern J. The antimicrobial activity of phenoxyethanol in vaccines. ***Lett Appl Microbiol*** 1994; **18**: 115-116.

doi: 10.1588/medver.2007.04.00145

"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."

While your reporting accurately reflects what the IOM addressed in its report and its key findings, we note that this IOM committee failed to address the issue of cumulative sub-acute mercury poisoning and the clinical effects of this cumulative sub-acute mercury poisoning on those repeatedly immunized with Thimerosal-preserved vaccines as most all were prior to 2000 since the reduced-Thimerosal vaccines did *not* start to become available until 2000 and, *because the existing in-date Thimerosal-preserved vaccines were not recalled but allowed to be used*, there was no precipitous decrease in the maximum dose that children received or could receive.

"The Committee stated 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.'"[Let-3]

While we find that it is laudable that you reported this "*Committee*" statement, we note that you failed to mention that the federal government and the vaccine makers, *by leaving existing Thimerosal-preserved vaccine stocks on the market after the "reduced Thimerosal" vaccines became available*, knowingly choose *not* to "… '*reduce mercury exposure of infants and children as much as possible*.'"

"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]

[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, http://www.nap.edu/catalog/10208.html.

[Let-4] IOM (Institute of Medicine). Immunization Safety Review: Vaccines and Autism. Washington, DC: National Academy Press, 2001, http://www.nap.edu/catalog/10997.html.

"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 methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom)."

First we agree that as written, the epidemiological studies cited here "***consistently provided evidence of no association between thimerosal-containing vaccines and autism***."

However absence of evidence of an association in an epidemiological study is *not* proof of the absence of an association.

Second, we note that this IOM report:

- Ignored evidence of an association between Thimerosal and other neurodevelopmental disorders reported in the only study that studied a population of children vaccinated according to the U.S. vaccination schedule (*Verstraeten et al., 2003*), and
- Failed to address the ever growing body of toxicological evidence that clearly demonstrated that repeatedly injecting pregnant women, newborns, babies, children and adults with 0.25- to 1- mL does of vaccine formulations containing 0.003% to 0.01% Thimerosal (49.55% mercury by weight), effectively about 0.0016% to 0.005% mercury by weight, mercury-poisons all who are injected with these vaccines to some degree.

Third, we have examined all of these epidemiological studies to the extent possible (because the refusal or inability of the authors to provide all of the data required to review them completely) and found that each seems to have been intentionally designed *not* to find evidence of an association between the Thimerosal being injected and the adverse outcomes being observed.

doi: 10.1588/medver.2007.04.00145

Based on the preceding realities, we must conclude that the reported "non-positive" findings reported by these studies must be completely discounted.

"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."

Since neither the IOM not you have provided any substantive data to support the statements made by the IOM or any references to any other peer-reviewed published studies that have examined any of the studies cited, we must conclude that the negative comments reported were simply concocted out of thin air and reject the characterizations assigned to these reports.

From a design and execution point of view, these studies were better designed and more properly executed that the studies the IOM found pertinent.

Moreover, since the authors of these studies were willing and able to provide the data they used for independent review, we find that these studies should have been accepted and, contrary to the IOM's position, the other epidemiological studies should have been rejected because there was/is no way for all of the data used in them to be independently evaluated to confirm the findings reported – because of this lack of independent repeatability, as scientists, we must consign those studies the IOM used to the dustbin reserved for "non-reproducible results" until such time as they can be independently replicated. .

Thus, as scientists, we accept the findings reported by the Geiers and Blaxill because those among us with a fundamental understanding of population statistics and differential effect assessment in noisy data sets had no problem with the study designs, the statistical treatments used, or interpreting the results reported.

"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*)."

While we disagree with the FDA conclusions and again note that the IOM failed to properly consider, *much less address*, the body of peer-reviewed toxicological evidence and the root issue of the link between the level of Thimerosal (49.55% mercury) injected and the incidence of the recognized symptoms of clinical mercury poisoning, including those clinical mercury-poisoning symptoms that are used to diagnose a given autistic spectrum disorder (ASD) (or pervasive developmental disorder [PDD]) as well as those clinical mercury-poisoning symptoms that are used to diagnose DSM autism.

In this epidemiological study, the authors' apparently *knowingly* confounded the increase in the reporting of autism cases (caused by the inclusion of groups of children previously excluded from the databases they were using for this study) by incorrectly considering this reporting increase as an increase in the incidence rates for autism cases.

In addition to having trouble obtaining the data they used so that it could be independently evaluated, we also note this paper failed to report the clear conflicts of interest of all of its authors.

Based on all of the preceding, we find that your stated conclusions, *which:*

- *Rely on flawed epidemiological studies and*
- *Ignore the ever growing body of toxicological evidence that clearly supports the reality that injecting mercury into human beings mercury-poisons all of them to some degree and, for those whose mercury detoxification mechanisms are, for whatever reasons, less effective than the average person's mercury detoxification mechanisms, mercury poisons these to the point that they exhibit the clinical symptoms of mercury poisoning*,

are *not* supported by any sound toxicological science of which we are aware or that you have provided in this letter to **CoMeD**.

doi: 10.1588/medver.2007.04.00145

"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 al., 2006)."[36]

First, we again note that Fombonne has refused repeated written and verbal (telephone message) requests by the **CoMeD** Science Advisor and other qualified independent scientists to provide all the key data upon which this paper is based so that that data can be independently evaluated and either verify or disprove this paper's reported findings.

In addition, Dr. Fombonne failed to disclose all of his conflicts of interest, including, but not limited to, his being named (and paid) as an "expert" in several legal cases where Thimerosal-related vaccine damage claims are being adjudicated.

Thus, until the data used are made available to independent research scientists for critical evaluation, this currently unsubstantiable paper and its unconfirmed published findings should be discounted and *not* used in any governmental decision-making process including your evaluation of the **CoMeD** citizen petition.

Furthermore, when **CoMeD**'s Science Advisor critically evaluated[37] the little data and information that was included in Fombonne *et al*.'s paper,[36] he found that the data provided failed to support the model used or the conclusions reported in it.

Based on our review, we find that the valid data points for grades "1" through "10" (excluding the invalid data points for grades "11," where the authors inappropriately adjusted the number of PDD cases rather than discarding that data point because, *as they admitted*, no valid denominator could be determined, and grade "K," where the denominator used was obviously biased by under ascertainment) support an increase in the incidence rate for total PDD cases from grades "10" through "4" (containing children *nominally* born in 1988 through 1994, who received increasing amounts of Thimerosal-containing vaccines) and a decrease in the incidence rates for total PDD cases in grades "3" through "1" (containing children *nominally* born in 1995 through 1998, who were given a significantly lower levels of Thimerosal-containing vaccines).

Hopefully, after you have read and evaluated **CoMeD**'s scientific assessment[37] of the Fombonne *et al*. paper,[36] you will see that the valid data values do provide evidence of a correlation between the increase and the decrease in level of Thimerosal exposure and the corresponding increase and decrease in the total PDD incidence values reported.

To sum up, the valid data points[37] in the Fombonne *et al*. paper[36] support **CoMeD**'s views and *not* the views you have represented that it supports based on the findings it reports.

"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."

First, we note that Parker *et al*., like the 2004 IOM report, dismissed those epidemiological studies that did show evidence of a link between Thimerosal-containing vaccines and ASDs with a glib, but unsubstantiated:

"Epidemiologic studies that support a link demonstrated significant design flaws that invalidate their conclusions."

Thus, we find the evaluations by Parker *et al*. were fundamentally prejudiced because they excluded those epidemiological studies that supported a link without providing a sound scientific for rejecting the studies they excluded or, *for that matter*, a sound scientific verification of the validity of the non-positive studies that they included in their evaluation.

Based on these findings, we conclude that, Parker *et al*. does *not*, as you claim, actually support your "*conclusion*" just as an in-depth review of Fombonne et al.[36] does *not* support your "*conclusion*."

"On the other hand, it is well established that vaccines have widespread, life-saving benefits."

---

[36] Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. Pervasive developmental disorders in Montreal, Quebec, Canada: Prevalence and links with immunizations. ***Pediatrics*** 2006 July; **118**(1): e139-e150.

[37] So that all may read that review, we have included a copy of this in-depth scientific assessment with this review of the letter you provided to CoMeD as **Appendix A, "Thimerosal Causes Mercury Poisoning X - Link Between Thimerosal and Pervasive Developmental Disorders [Draft Rebuttal to Fombonne et al.'s 'Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations']"** without its appendices (the appendices may be reviewed in the full article posted at: http:/www.mercury-freedrugs.org/docs/060827_PGK'sCmmnts_CanadianEpidemioStudy_Pediatrics-Full-b.pdf).

doi: 10.1588/medver.2007.04.00145

We simply note that the issue of the "*widespread, life-saving benefits*" of vaccines is *not* an issue that is germane to the issues we have raised in the **CoMeD** petition.

"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."

Again, your statement ignores your non-dischargeable higher duties:

- Your explicit mandate to do whatever you have the authority to do to reduce the risk of adverse reactions in childhood vaccines (as per **42 U.S.C. Sec. 300aa-27**) as well as your implicit mandate to, *at a minimum*, take similar actions for all vaccines and other biological drug products.
- Your explicit legal responsibility to ensure that you only license vaccines that have met all regulatory requirements including the requirement to prove that the preservative used is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" **(21 CFR § 610.15(a)**).

Regardless of what arguments you use to justify your obvious knowing actions, you have failed to comply with the applicable, laws and statutes that regulate your legal conduct and/or require the firms you are supposedly regulating to meet a clear requirement before you can legally license or approve, or continue to license or approve, a vaccine or other biological drug product.

Since: **a)** the Supreme Court has unanimously ruled in 1988 in *Berkovitz*[1] that you have no discretion to knowingly allow a drug manufacturer *not* to comply with a clear regulation, **b)** you have repeatedly testified that the manufacturers have *not* conducted the required toxicological studies to establish that the preservative level of Thimerosal administered, or, for that matter any lower level is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient," your current actions have you:

- Attempting to deny this petition without addressing the clear underlying issues raised in that citizen petition,
- Refusing to compel the vaccine makers to conduct the requisite toxicology studies required for them to comply with **21 CFR § 610.15(a)**,
- Lacking any proof of safety that meets the "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" criterion, continuing to license new Thimerosal-preserved influenza vaccines (like the October 5, 2006 approval of FluLaval), and
- *With full access to the thousands of adverse reaction reports for hypersensitivity to Thimerosal including those submitted to CBER in the years prior to the creation of the VAERS database*,
  - Persisting in refusing to prohibit the use of Thimerosal, *a highly toxic, teratogenic, mutagenic and immunogenic compound at the sub-part-per-million level (making it at least two orders of magnitude worse than more familiar teratogens, like Thalidomide)*, or any other mercury-based compound in the manufacture of any drug product,
  - Refusing to reduce the risk of adverse reactions in childhood vaccinations by requiring all vaccine manufacturers to remove Thimerosal from all childhood vaccines and, thereby, comply with **42 U.S.C. Sec. 300aa-27(a)(2)**, and
- Continuing to condone the mercury poisoning of all fetuses, newborns, babies, children, adolescents, adults and the elderly by the Thimerosal-containing drugs, including vaccines, administered to them or, in the case of the fetuses, their pregnant mothers. .

Given the preceding substantiated realities, the **CoMeD** reviewers find that you are knowingly holding yourselves to be above the law and, hopefully, the courts will recognize your actions for what they are and take the appropriate actions.

"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]

[Let-5] Plotkin, Stanley A. et al., Vaccines, 4th Edition, Chapter 17 (2004), http://intl.elsevierhealth.com/catalogue/title.cfm?ISBN=0721696880.

First, we find that these "*recent analyses*" are at odds with the actual published values reported in a 2006 article[20] covering the period from 1987 to 2000.

doi: 10.1588/medver.2007.04.00145

Rather than discuss that, *as you admit*, estimated data, we are including the data table containing the published historical data used that were used to assess the "effectiveness" of the influenza vaccine in this response as **Reviewers' Table 1** on the next page.

Based on the government's own historical data for the years reported (**see**: **Reviewers' Table I**), Geier *et al*.[20] found that the influenza vaccines are *not* effective in either protecting those inoculated from contracting influenza or in stopping the spread of influenza.

Lest you or the reader think that these findings are "new," we would suggest that you read the other peer-reviewed published articles referenced by the Geier *et al*. and read the review of the FDA Consumer magazine article[38] by the **CoMeD** Science Advisor, which has been included as **Appendix B** to **CoMeD**'s review of this letter.

"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."

First, while the **CoMeD** reviewers agree that there are "*severe complications and deaths related to influenza*" in a few children each year (**see Reviewers' Table 2**), we note that you correctly said these were "*related to influenza*" and *not* influenza deaths *per se*.
Based on history, *on average*, only about 12 (6 – 18) "*children under 23 months of age*" die each year from reasons that are influenza-related.

Since about 4 million children are born each year, these deaths translate to an influenza-related mortality rate of about 1.5 deaths per million children.

While it is sad that any child should die, it is clear that recommending that all be vaccinated with a vaccine for a disease with this mortality rate would lead to an outcome such that the cost per death prevented, *presuming 2 doses of vaccine at 6 months and 7 months at $ 25.00 per dose, 1 dose at about 18 months at a cost of $ 25.00 per dose, and full vaccination*, would be on the order of $ 25 million dollars.

From this data, *even if effective*, the influenza vaccination of all children 6 months to 23-months of age is *obviously not* cost justified.

However, published research [24,39] has shown that the current influenza vaccines are *not* effective in preventing young children from contracting influenza.

Specifically, Jefferson *et al*.[24] found that, for children 2 years of age and under, influenza vaccination was no better than a placebo injection in preventing a healthy child from getting influenza.

Thus, we find that not only is the influenza vaccination program for children 6 months to 23 months unjustified on the basis of cost, this program is also *not* justifiable because vaccinating children in this age group is clearly ineffective.

Based on the preceding findings that the influenza vaccines are *not* effective for children under 2 years of age as well as for the American public in general, we hope that you will stop this program on this basis alone.

---

38 "Influenza: Vaccination Still the Best Protection" by Linda Bren, FDA Writer-Editor. Online "September-October 2006" ***FDA Consumer magazine***. http://www.fda.gov/fdac/features/2006/506_influenza.html.

39 Maeda T, Shintani Y, Nakano K, Terashima K, Yamada Y. Failure of inactivated influenza A vaccine to protect healthy children aged 6-24 months. ***Pediatr Int*** 2004; **46**: 122-125.

doi: 10.1588/medver.2007.04.00145

Reviewer's Table 1. A summary of the raw data employed for analysis in the present study[20]

Year	Estimated United States Population[1]	Total Net Number of Influenza Vaccine Doses Distributed[2]	Influenza Vaccine Percent Population Coverage [IVPPC]	Influenza Death Rate[3] (per 100,000 people) [Total Number]	Influenza Case Rate[3] (per 100 people) [Total Number]	Influenza First-Listed Hospital Discharge Rate[3] (per 10,000 people) [Total Number]
1979[4]	225,055,487	18,270,794	8.1	0.3	-	-
1980	227,224,681	12,425,890	5.5	-	-	-
1981	229,465,714	19,829,170	8.6	1.3	-	-
1982	231,664,458	16,959,690	7.3	-	**33**	-
1983	233,791,994	17,877,970	7.6	0.6	38	-
1984	235,824,902	19,179,060	8.1	-	45	-
1985	237,923,795	20,700,761	8.7	0.9	40	-
1990	249,464,396	27,076,206	11	-	43	1.8
1991	252,153,092	32,809,662	13	0.4	**52**	1.0
1992	255,029,699	40,352,367	16	-	43	0.5
1993	257,782,608	42,980,814	17	0.4	**52**	1
1994	260,327,021	60,084,728	23	-	35	1.2
1995	262,803,276	36,512,538	14	0.2	41	0.7
1996	265,228,572	38,915,520	15	0.3	36	0.8
1997	267,783,607	40,996,883	15	0.3	-	0.7
1998	270,248,003	48,080,122	18	0.6	-	1.3
1999[5]	272,690,813	60,468,427	22	0.6	-	1.4
2000	281,421,906	65,582,650	23	0.6	-	1.4
			Mean ± std	0.5 ± 0.3 [1,269 ± 786]	38 ± 13 [94 ± 3.4 million]	1 ± 0.5 [25,667±12,323]

[1] Data obtained from the United States' Census Bureau

[2] Data obtained from the Biologic Surveillance Summaries of the Centers for Disease Control and Prevention

[3] Data obtained from the National Center for Health Statistics

[4] Estimates for 1979 through 1998 use International Classification of Diseases, 9th Revision (ICD-9) coding

[5] Estimates for 1999 through 2000 use International Classification of Disease, 10th Revision (ICD-10) coding

Further, with respect to your assertion of a "*theoretical risk of vaccine causing autism*," ***which misstates the causal risk as "vaccine" when we have shown that that the risk is clearly the "Thimerosal" in the vaccine***, we note that you have failed to present toxicological studies that have proven that this risk is "*theoretical*" and, ***contrary to your assertion***, our review of the valid epidemiological data published by Fombonne ***et al***.[36] has clearly shown that there is a link between the maximum level of Thimerosal exposure from vaccines and the number of PDD cases found.

Finally, we note that the **CoMeD** petition has presented ample evidence that Thimerosal causes mercury poisoning in human tissues at levels more than 5,000 times lower than the 100-ppm (0.01%) level of Thimerosal in most Thimerosal-preserved vaccines and the recent paper by Parran ***et al***.[18] has extended that toxic differential to more than 100,000 times lower than the vaccine level when the researchers confirmed neuron cell death (apoptosis) in developing human neuron meshes from Thimerosal exposures below 0.001 ppm (< 1 part-per-billion; 0.0000001%).

Additionally, a 2005 paper by Al-Salech ***et al***. [40] established that even some of the inorganic mercury applied topically at low levels (< 1 ppm) can accumulate in and damage the brain.

[40] Al-Saleh I, El-Doush I, Shinwari N, Al-Baradei R. Does low mercury containing skin-lightening cream (Fair & Lovely) affect the kidney, liver, and brain of female mice? ***Cutaneous & Ocular Tox*** 2005; **24**:11-29.

doi: 10.1588/medver.2007.04.00145

Reviewers' Table 2. Number of influenza deaths per year in children

Year	<1 year-old	1-4 years-old	5-14 years-old	0-14 years-old
1979	9	8	8	25
1981	13	8	12	33
1983	6	8	3	17
1985	7	6	7	20
1987	8	6	1	15
1989	12	8	14	34
1991	16	15	11	42
1993	10	14	13	37
1995	7	7	7	21
1996	15	3	8	26
1997	12	10	13	35
1998	6	3	14	23
1999	13	12	11	36
2000	9	10	11	30
2001	7	6	12	25
Mean ± Std	10.0 ± 3.2	8.3 ± 3.5	9.7 ± 3.7	27.9 ± 8.0[2]
Median	9.0	8.0	11.0	26

[1] Data obtained from the National Center for Health Statistics
[2] Mean-based death rate for children aged "0"–14 of about 0.5 deaths per million children

Based on all of the preceding, we must reject your "***2.*** *For the vaccines that still contain thimerosal, the evidence favors rejecting your allegations about risks, and the benefits are lifesaving and well-established*" because it is *not* supported by the scientific information we have provided in our petition and this review, or, *for that matter*, by the valid epidemiological data from the recent epidemiological study by Fombonne et al.[36] that you have chosen to cite.

"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.*"

Since lethal toxicity for Thimerosal has been established at levels below 0.0000001% (< 0.001 ppm; < 1 ppb) in 2005,[18] we find that your statement is at odds with the current state of knowledge for Thimerosal in drug products.

In addition, since the **CoMeD** petition reported lethal toxicity to human skin and notochord tissues at Thimerosal below 0.0002% (< 0.02 ppm; <20 ppb), we find that your statement is at clearly odds with reality for Thimerosal in drug products, including vaccines.

For inorganic mercury, we note that the **CoMeD** petition found and reported developing-neural-cell-mesh toxicity to inorganic mercury (Hg^{2+}) at levels below 0.0002% (< 0.02 ppm; <20 ppb).

Based on these findings, we conclude that your, "*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*," is *not* supported by the scientific evidence.

"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."

First, reviewing the limited literature on phenylmercuric acetate (PMA), we find that your presentation has failed to present an accurate picture of its toxicity.

doi: 10.1588/medver.2007.04.00145

Factually, you present no clearance data that establishes that all the PMA is "*completely converted to the inorganic form within days of dosing*" and excreted from the body.

Since the literature clearly shows that PMA crosses the blood-brain and placental barriers and that the "*inorganic form*" of mercury that is present in the brain has a half-life of more than 20 years, we find that all you have established is that the level of "inorganic mercury" in the brain should be even higher than it is for dosed ethyl mercury compound Thimerosal, which recent (2004) experiments in developing baby monkeys, reported in 2005[41], have shown is up to three times higher than for the same level of dosed methylmercury hydroxide.

Moreover, we find your "*Thus, the toxicity caused by PMA is similar to inorganic mercury, with the kidney as the target organ*" is at odds with Clarkson,[42] who stated, "The fact that much lower dietary doses of phenylmercury than of inorganic mercury can lead to the same degree of damage can be quantitatively accounted for by the difference in efficiency of gastrointestinal absorption of the two compounds" – clearly indicating that the toxicity of PMA differs from that of "*inorganic mercury*."

In addition, since PMA, *like Thimerosal and other ethyl and methyl mercury compounds*, crosses the blood-brain and placental barriers, PMA has the potential to damage the central nervous system in the fetus, child and adult.

Furthermore, consulting the J.T. baker's year-2000 MSDS for PMA, we find, under "**Emergency Overview**" that MSDS (**see** page S-R-43) states, with underlining added for emphasis:

"**DANGER! MAY BE FATAL IF SWALLOWED. HARMFUL IF INHALED OR ABSORBED THROUGH SKIN. CAUSES SEVERE IRRITATION TO EYES, SKIN AND RESPIRATORY TRACT; MAY CAUSE BURNS. MAY CAUSE ALLERGIC SKIN REACTION. MERCURY COMPOUNDS AFFECT THE KIDNEYS AND CENTRAL NERVOUS SYSTEM. BIRTH DEFECT HAZARD. CAN CAUSE BIRTH DEFECTS. COMBUSTIBLE SOLID**."

indicating that, in addition to being a hazard to the kidneys, PMA is hazardous to the central nervous system and is a teratogen and mutagen.

Based on the preceding, we must conclude that your characterization of PMA is, at best, misleading and that PMA's toxicity is "similar" to that of Thimerosal.

"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."

While we see where you obtained the value you used, we note that, *since your NOEL value was derived from a rat study*, in 1996 the EPA[43] reported that the ADI value that should be used in humans is "0.08 µg/kg/day" PMA, a value "two" orders of magnitude lower than the one you chose to use.

Deferring to the EPA's understanding of the toxicity differences between rats and humans, we find that this is the value you should have used in your calculations for safety and not the "*8.4 µg/kg/day PMA*" that you chose to use.

"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."

We agree with your assessment that the most conservative value should be used for "risk estimation," but again note that that value is the 1996 EPA ADI value of "0.08 µg/kg/day" for PMA.

---

41 Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal. ***Environ Health Perspect***. 2005 Aug; **113**(8):1015-1021.

42 Clarkson TW. The biological properties and distribution of mercury. ***Biochem J***. 1972 Nov; **130**(2):61P-63P.

43 http://www.epa.gov/iriswebp/iris/subst/0089.htm

doi: 10.1588/medver.2007.04.00145

"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."

The **CoMeD** reviewers have no problem with your calculated dose.

However using the 1996 EPA ADI value for safe PMA intake, 0.08 µg/kg/day, as you should have done, we find that the daily dose you calculated, "*0.87 µg/kg/day*" for your "*50-kg individual*" exceeds the ADI level by more than a factor of 10!

Based on the preceding realities, we must conclude that, even at one-tenth the daily dose you have calculated, the daily exposure would exceed the EPA's ADI and that, therefore, this data establishes that the use of PMA as a preservative in these products *cannot* be presumed to be safe.

Therefore, you should have required/require the manufacturers of these products to have proven/prove safety in appropriate scientifically sound and appropriate toxicological tests, including reproductive toxicity tests of the formulation in, *at a minimum*, a primate species having comparable mercury-poisoning sensitivity to humans with a dose 100 times the maximum dose allowed on the label so that the extrapolation to humans would be much more valid than extrapolating from the rat, which is known to be less than sound in many cases.

In the absence of the appropriate toxicological proof of safety, we find that you should suspend the approvals of these products until the manufacturers can:

- Prove the safety of the use of PMA as a preservative, or
- Reformulate them with a safer preservative system, or
- Remove the preservative from the formulation and switch to single-dose packaging.

Reviewers' Table 2 – Text from J.T. Baker MSDS

MSDS Number: **P3268** * * * * * *Effective Date:* ***05/08/00*** * * * * * *Supercedes:* ***06/16/97***

PHENYLMERCURIC ACETATE

1. Product Identification

Synonyms: (Acetato) phenyl mercury; acetoxyphenylmercury; PMA; PMAC; PMAS
CAS No.: 62-38-4
Molecular Weight: 336.74
Chemical Formula: (CH3COO) HgC6H5
Product Codes: T781

2. Composition/Information on Ingredients

Ingredient	CAS No	Percent	Hazardous
Mercury, (acetato-O)phenyl-	62-38-4	98 - 100%	Yes

3. Hazards Identification

EmergencyOverview

DANGER! MAY BE FATAL IF SWALLOWED. HARMFUL IF INHALED OR ABSORBED THROUGH SKIN. CAUSES SEVERE IRRITATION TO EYES, SKIN AND RESPIRATORY TRACT; MAY CAUSE BURNS. MAY CAUSE ALLERGIC SKIN REACTION. MERCURY COMPOUNDS AFFECT THE KIDNEYS AND CENTRAL NERVOUS SYSTEM. BIRTH DEFECT HAZARD. CAN CAUSE BIRTH DEFECTS. COMBUSTIBLE SOLID.

Potential Health Effects

Inhalation:
Causes irritation to the respiratory tract. Symptoms include sore throat, coughing, pain, tightness in chest, breathing difficulties, shortness of breath and headache. Pneumonitis may develop. Can be absorbed through inhalation with symptoms to parallel ingestion. Inhalation of large amounts can cause severe and potentially lethal pulmonary edema.
Ingestion:
Highly Toxic! Average lethal dose for inorganic

doi: 10.1588/medver.2007.04.00145

mercury salts is about 1 gram. May cause burning of the mouth and pharynx, abdominal pain, vomiting, corrosive ulceration, bloody diarrhea. May be followed by a rapid and weak pulse, shallow breathing, paleness, exhaustion, central nervous system problems, tremors and collapse. Delayed death may occur from renal failure.

Skin Contact:
Causes irritation and burns to skin. Symptoms include redness and pain. May cause skin allergy and sensitization. Can be absorbed through the skin with symptoms to parallel ingestion.

Eye Contact:
Causes irritation and burns to eyes. Symptoms include redness, pain, blurred vision; may cause serious and permanent eye damage.

Chronic Exposure:
Chronic exposure through any route can produce central nervous system damage. May cause muscle tremors, personality and behavior changes, memory loss, metallic taste, loosening of the teeth, digestive disorders, skin rashes, brain damage and kidney damage. Can cause skin allergies and accumulate in the body. Repeated skin contact can cause the skin to turn gray in color. Teratogen: can damage the developing fetus and decrease fertility in males and females.

Aggravation of Pre-existing Conditions:
Persons with nervous disorders, or impaired kidney or respiratory function, or a history of allergies or a known sensitization to mercury may be more susceptible to the effects of the substance.

4. First Aid Measures

Inhalation:
Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention immediately.

Ingestion:
Induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. Get medical attention immediately.

Skin Contact:
Immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Get medical attention immediately. Wash clothing before reuse. Thoroughly clean shoes before reuse.

Eye Contact:
Immediately flush eyes with plenty of water for at least 15 minutes, lifting lower and upper eyelids occasionally. Get medical attention immediately.

5. Fire Fighting Measures

Fire:
Flash point: > 38C (> 100F)

Combustible solid.

Explosion:
Fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard.

Fire Extinguishing Media:

Dry chemical, foam or carbon dioxide. Do not allow water runoff to enter sewers or waterways.

Special Information:

In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode. Smoke may contain toxic mercury or mercuric oxide.

6. Accidental Release Measures

Remove all sources of ignition. Ventilate area of leak or spill. Wear appropriate personal protective equipment as specified in Section 8. Spills: Clean up spills in a manner that does not disperse dust into the air. Use non-sparking tools and equipment. Reduce airborne dust and prevent scattering by moistening with water. Pick up spill for recovery or disposal and place in a closed container. US Regulations (CERCLA) require reporting spills and releases to soil, water and air in excess of reportable quantities. The toll free number for the US Coast Guard National Response Center is (800) 424-8802.

7. Handling and Storage

Keep in a tightly closed container. Store in a cool, dry, ventilated area away from sources of heat or ignition. Protect against physical damage. Store separately from reactive or combustible materials, and out of direct sunlight. Outside or detached storage is recommended. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.

8. Exposure Controls/Personal Protection

Airborne Exposure Limits:
- OSHA Acceptable Ceiling Concentration: mercury and mercury compounds: 0.1 mg/m3 (TWA), skin

- ACGIH Threshold Limit Value (TLV): inorganic and metallic mercury, as Hg: 0.025 mg/m3 (TWA) skin, A4 Not classifiable as a human carcinogen.

- ACGIH Biological Exposure Indices: total inorganic mercury in urine (preshift): 35 ug/g creatinine;

total inorganic mercury in blood (end of shift): 15 ug/l.

Ventilation System:

A system of local and/or general exhaust is recommended to keep employee exposures

doi: 10.1588/medver.2007.04.00145

below the Airborne Exposure Limits. Local exhaust ventilation is generally preferred because it can control the emissions of the contaminant at its source, preventing dispersion of it into the general work area. Please refer to the ACGIH document, *Industrial Ventilation, A Manual of Recommended Practices*, most recent edition, for details.

Personal Respirators (NIOSH Approved): If the exposure limit is exceeded, a full facepiece respirator with dust/mist filter may be worn up to 50 times the exposure limit or the maximum use concentration specified by the appropriate regulatory agency or respirator supplier, whichever is lowest. For emergencies or instances where the exposure levels are not known, use a full-facepiece positive-pressure, air-supplied respirator. WARNING: Air purifying respirators do not protect workers in oxygen-deficient atmospheres.

Skin Protection:

Rubber or neoprene gloves and additional protection including impervious boots, apron, or coveralls, as needed in areas of unusual exposure.

Eye Protection:

Use chemical safety goggles and/or full face shield where dusting or splashing of solutions is possible. Maintain eye wash fountain and quick-drench facilities in work area.

Other Control Measures:

There is insufficient data in the published literature to assign complete numerical SAF-T-DATA* ratings and laboratory protective equipment for this product. Special precautions must be used in storage, use and handling. Protective equipment for laboratory bench use should be chosen using professional judgment based on the size and type of reaction or test to be conducted and the available ventilation, with overriding consideration to minimize contact with the chemical.

9. Physical and Chemical Properties

Appearance: Coarse yellow-white, hygroscopic powder.
Odor: Acetic acid odor.
Solubility: 0.16g in 100g of water.
Density: No information found.
pH: No information found.
% Volatiles by volume @ 21C (70F): 0
Boiling Point: Not applicable.
Melting Point: 149C (300F)
Vapor Density (Air=1): No information found.
Vapor Pressure (mm Hg): 0 @ 20C (68F)
Evaporation Rate (BuAc=1): 0

10. Stability and Reactivity

Stability: Stable under ordinary conditions of use and storage.
Hazardous Decomposition Products: Carbon dioxide and carbon monoxide may form when heated to decomposition. Mercury compound may also be volatilized.
Hazardous Polymerization: Will not occur.
Incompatibilities: Strong oxidizing agents, sulfur, ammonia.
Conditions to Avoid: Heat, flames, ignition sources and incompatibles.

11. Toxicological Information

Toxicological Data:
Oral rat LD50: 41 mg/kg. Irritation, standard Draize, rabbit, eye: 50 ug/24H, severe. Investigated as a tumorigen, mutagen, reproductive effector.
Reproductive Toxicity:
All forms of mercury can cross the placenta to the fetus, but most of what is known has been learned from experimental animals. See Chronic Health Hazards.

--------\Cancer Lists\----------

	---NTP Carcinogen---		
Ingredient	Known	Anticipated	IARC Category
Mercury, (acetato-O)phenyl- (62-38-4)	No	No	None

12. Ecological Information

Environmental Fate:

When released into the soil, this material may leach into groundwater. When released into the soil, this material is not expected to evaporate significantly. When released into water, this material is not expected to evaporate significantly. This material has an experimentally determined bioconcentration factor (BCF) of less than 100. This material is not expected to significantly bioaccumulate. When released into the air, this material may be moderately degraded by photolysis. When released into the air, this material may be removed from the atmosphere to a moderate extent by wet deposition.

Environmental Toxicity:

For mercury: This material is expected to be toxic to aquatic life. The LC50/96-hour values for fish are less than 1 mg/l.

13. Disposal Considerations

Whatever cannot be saved for recovery or recycling should be handled as hazardous waste and sent to a RCRA approved waste facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

14. Transport Information

Domestic (Land, D.O.T.)
---

doi: 10.1588/medver.2007.04.00145

Proper Shipping Name:
PHENYLMERCURIC ACETATE
Hazard Class: 6.1
UN/NA: UN1674
Packing Group: II
Information reported for product/size: 25G

International (Water, I.M.O.)

Proper Shipping Name:
PHENYLMERCURIC ACETATE
Hazard Class: 6.1
UN/NA: UN1674
Packing Group: II
Information reported for product/size: 25G

15. Regulatory Information

--------\Chemical Inventory Status - Part 1\----------

Ingredient	TSCA	EC	Japan	Australia
Mercury, (acetato-O)phenyl- (62-38-4)	Yes	Yes	Yes	Yes

--------\Chemical Inventory Status - Part 2\----------

Ingredient	--Canada-- Korea	DSL	NDSL	Phil.
Mercury, (acetato-O)phenyl- (62-38-4)	No	Yes	No	Yes

--------\Federal, State & International Regulations - Part 1\----------

Ingredient	-SARA 302- RQ	TPQ	------SARA 313------ List	Chemical Catg.
Mercury, (acetato-O)phenyl- (62-38-4)	100	500*	No	Mercury comp

--------\Federal, State & International Regulations - Part 2\----------

Ingredient	CERCLA	-RCRA- 261.33	-TSCA- 8(d)
Mercury, (acetato-O)phenyl- (62-38-4)	100	P092	No

Chemical Weapons Convention: No TSCA 12(b): No
CDTA: No SARA 311/312: Acute: Yes Chronic: Yes
Fire: Yes Pressure: No Reactivity: No (Pure / Solid)

WARNING:
THIS PRODUCT CONTAINS A CHEMICAL(S) KNOWN TO THE STATE OF CALIFORNIA TO CAUSE BIRTH DEFECTS OR OTHER REPRODUCTIVE HARM.

Australian Hazchem Code: 2X
Poison Schedule: S7
WHMIS:
This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

16. Other Information

NFPA Ratings: Health: **3** Flammability: **1** Reactivity: 0

Label Hazard Warning:
DANGER! MAY BE FATAL IF SWALLOWED. HARMFUL IF INHALED OR ABSORBED THROUGH SKIN. CAUSES SEVERE IRRITATION TO EYES, SKIN AND RESPIRATORY TRACT; MAY CAUSE BURNS. MAY CAUSE ALLERGIC SKIN REACTION. MERCURY COMPOUNDS AFFECT THE KIDNEYS AND CENTRAL NERVOUS SYSTEM. BIRTH DEFECT HAZARD. CAN CAUSE BIRTH DEFECTS. COMBUSTIBLE SOLID.

Label Precautions:
No SAF-T-DATA Ratings have been developed for this product. Read and follow all warnings, precautions, instructions and other safety and handling information on the label and MSDS.
Keep away from heat and flame.
Do not breathe dust.
Keep container closed.
Use only with adequate ventilation.
Wash thoroughly after handling.
Do not get in eyes, on skin, or on clothing.

Label First Aid:
If swallowed, induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before reuse. In all cases get medical attention immediately.

Product Use:
Laboratory Reagent.

Revision Information:
New 16 section MSDS format, all sections have been revised.

Disclaimer:
****
Mallinckrodt Baker, Inc. provides the information contained herein in good faith but makes no representation as to its comprehensiveness or accuracy. This document is intended only as a guide to the appropriate precautionary handling of the material by a properly trained person using this product. Individuals receiving the information must exercise their independent judgment in determining its appropriateness for a particular purpose.

MALLINCKRODT BAKER, INC. MAKES NO REPRESENTATIONS OR WARRANTIES, EITHER EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE WITH RESPECT TO THE INFORMATION SET FORTH HEREIN OR THE PRODUCT TO WHICH THE INFORMATION REFERS. ACCORDINGLY, MALLINCKRODT BAKER, INC. WILL NOT BE RESPONSIBLE FOR DAMAGES RESULTING FROM USE OF OR RELIANCE UPON THIS INFORMATION.
****

Prepared by: Environmental Health & Safety
Phone Number: (314) 654-1600 (U.S.A.)

doi: 10.1588/medver.2007.04.00145

Furthermore, we find your "*assuming that intranasal exposure in humans is comparable to dietary exposure in rats*" to be highly unlikely because the exposure pathway: **a)** provides almost direct access to the brain, and **b)** bypasses the stomach where significant solvolytic degradation of the PMA should occur, and note that you have presented no studies or citations to lend credence to your view.

"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."

Again we note that all that has been demonstrated in the studies you cite is rapid clearance from the blood and urine and *not* rapid or complete clearance from the body and, *as human studies have reported*,[27] the "inorganic mercury" that is generated in the brain probably has a "22-year" half-life – clearly indicating slow clearance of "tissue bound" inorganic mercury.

We remind you that, *in spite of a "7-day" half-life in the blood*, Burbacher *et al*.[26] noted, *in a study on developing baby monkeys*, the half-life of the organic mercury in the brain was about a month and there was a significant long-term accumulation (> 4 months) of "inorganic mercury" from the brain's metabolizing that organic mercury into 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."

Given the exposure level in 6-year olds can easily be 25 times the EPA's safe ADI and developing children have been shown to be more sensitive to being poisoned by mercury than adults, we find your reassuring remarks to be, at best, unconvincing.

"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."

As was the case for the nasal sprays, we agree with your calculation of the dose.

However, using the EPA's ADI, "0.08 µg/kg/day" for PMA, as you should have done, we find that the daily level exceeds that ADI by a factor of about "7" for your "*50-kg person*," and, *for a 5-kg child who might receive such*, the daily level exceeds the EPA's ADI by a factor of about "69."

Obviously, based on these findings, the use of PMA in these ointments is *not* sufficiently safe in the EPA's view.

Therefore, you should have required/require the manufacturers of these products to have proven/prove safety in appropriate scientifically sound and appropriate toxicological tests, including reproductive toxicity tests of the formulation in, *at a minimum*, a primate species having comparable mercury-poisoning sensitivity to humans with a dose 100 times the maximum dose allowed on the label so that the extrapolation to humans would be much more valid than extrapolating from the rat, which is known to be less than sound in many cases.

In the absence of the appropriate toxicological proof of safety, we find that you should suspend the approvals of these products until the manufacturers can:

- Prove the safety of the use of PMA as a preservative, or
- Reformulate them with a safer preservative system, or
- Remove the preservative from the formulation and switch to single-dose packaging.

"Therefore, we believe that the use of PMA in ophthalmic products does not pose a threat to human health."

As our in-depth assessment has clearly shown, your belief "*that the use of PMA in ophthalmic products does not pose a threat to human health*" is *neither* appropriate *nor* supported by the EPA's ADI, their best guess as to a safe daily intake exposure level for adults.

doi: 10.1588/medver.2007.04.00145

"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."

We respectfully disagree with your assessment of the "*T-lymphocyte-mediated hypersensitivity*" caused by Thimerosal.

Since, *at sub-ppm levels*, Thimerosal has been shown to be a strong immune-system "activator" and autoimmune-"triggering agent" in humans, it is clear that the human body's immune system treats it as a "poison" (substance with an inherent property that tends to impair health) and that Thimerosal also directly damages the human immune system (by inducing autoimmunity).

Though you later allege that Thimerosal is *not* an adjuvant,[44] Eli Lilly officials clearly hold a somewhat different view.[45]

Speaking of Thimerosal at the 1999 Lister Hill conference on Thimerosal in vaccines, Eli Lilly Senior Research Scientist Dr. Jeffrey Englhardt stated (with underlining added for emphasis):

> "Also as mentioned earlier, thimerosal is a very exquisite antigen, not only in people but also in guinea pigs and rabbits, and it is also a dermal irritant as was described in some of the earlier literature when thimerosal was used as a contact lens solution preservative. The ethylmercuric chloride is the purported allergen that's responsible for these phenomena not only in people but also in animals, and one of the disparities from the animal studies that's been identified is that, unlike people that can occasionally have a systemic hypersensitivity reaction, those particular phenomena have not been identified in either the rabbit or the guinea pig studies."[46]

Since, *in pharmacology*, an *antigen* is any commercial substance that, when injected or absorbed into animal tissues, stimulates the production of antibodies, it is clear that, since Thimerosal is a strong immunogen and an antigen, when added to a vaccine in an injected-vaccine formulation, it is also an adjuvant because that vaccine formulation will elicit a more marked immune response than the same formulation without the Thimerosal.

In addition, as Dr. Englhrdt admits, Thimerosal can trigger a "systemic hypersensitivity reaction."

Further, we cite the Pittman Moore experience (**CoMeD** citizen petition, page P-31):

> "In 1935, in a letter from the Director of Biological Services, of the Pittman-Moore Company to Dr. Jamieson of Eli Lilly, **'we have obtained marked local reaction in about 50% of the dogs injected with serum containing dilutions of Merthiolate, varying in 1 in 40,000 to 1 in 5,000** … **no connection between the lot of serum and the reaction.** In other words, **Merthiolate is unsatisfactory as a preservative for serum** intended for use on dogs ... I might say that we have tested Merthiolate on humans and find that it gives a more marked local reaction than does phenol and tricresol.**'**[29]**"**

as evidence from 1935 that a 0.0025% Thimerosal (also known as Merthiolate) in a biological preparation can cause marked local reactions at levels one fourth the 0.01% found in most Thimerosal-preserved vaccines.

In addition, we note that, *in addition to being highly toxic*, Thimerosal is a teratogen, carcinogen, mutagen, immunogen and autoimmunogen. [**Note: See Appendix C** for MSDS documents from Eli Lilly & Co. (1999) and Sigma Chemicals Co. (2002) for more detailed general toxicity information on Thimerosal.]

However, we do agree with your assessment that "*the data are insufficient … to set limits based on toxicity*."

---

44 Adjuvant is a substance mixed with an immunogen in order to elicit a more marked immune response.

45 CoMeD citizen petition's endnote 7, Transcript from the two-day "NATIONAL VACCINE ADVISORY COMMITTEE SPONSORED WORKSHOP ON THIMEROSAL VACCINES," held on August 11-12, 1999, at the National Institutes of Health, Lister Hill Auditorium in Bethesda, Maryland.

46 *loc. cit.*, day1, pages 95-96.

doi: 10.1588/medver.2007.04.00145

"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 or systemic toxicity under the conditions of this study. Only one dose level of thimerosal was used, which precludes estimation of a toxicological dose response relationship. Therefore, this study was not further considered for human exposure comparisons."

Since there are about 20 drops per mL and the solution was 0.001% (10 µg/mL), the 6 drops dosed per day translates into a daily Thimerosal dose of about 0.3 µg (0.15 µg of mercury), 1/167th the adult dose and 1/83rd the dose for children 3 and under.

If you presume that an adult weighs 50 kg and is injected with 50 µg of Thimerosal, the young child weighs 3 kg and is injected with 25 µg of Thimerosal, and the rabbit weights 1 kg, the initial post-dosing Thimerosal concentration in the rabbit will be 0.0003 ppm while, for the typical vaccine, the initial post-injection Thimerosal concentration in the 50-kg adult will be 0.001 ppm and, in the child, 0.0083 ppm.

This means that the rabbits were dosed with roughly 1/3 the adult dose and roughly 1/28th the child's dose.

Based on the concentration and species differences, we agree with you that this study was *not* suitable "*for human exposure comparisons*."

"Mercury is present in thimerosal at a level of approximately 50% mercury by weight. This yields a maximum mercury concentration of approximately 0.005% in thimerosal-containing ophthalmic products. The recommended usage for these products is 1 drop in each eye 4 times a day. As an exposure estimate, an extreme usage of these products would be 2 drops in each eye every hour for 24 hours. At a volume of 50 µl per drop, the total daily exposure to mercury would be 0.25 mg/day or 5 µ/kg/day in a 50-kg person. The NOEL of 1.0 mg/kg/day for chronically administered thimerosal in rats (equivalent to 1,000 µg/kg) is over 200 times the estimated exposure to humans based on an exaggerated dose regimen via the ophthalmic route. Therefore, we believe that the use of thimerosal in ophthalmic products does not pose a threat to human health."

We accept your estimation of the maximum dose of Thimerosal as 25 mg/day or 5 µg/kg/day in a 50-kg person.

However, we again dispute your use of the NOEL for rats because we find that you should have used the EPA's estimated NOEL for "methylmercury" based on human consumption of fish containing protein bound methylmercury (0.1 µg/kg/day) because:

- That EPA limit it is a limit based on human consumption studies and
- Large-animal studies have shown that the overall toxicity of ethyl mercury, Thimerosal's solvolysis product, is about the same as that of methyl mercury.

Moreover, since Burbacher *et al*.[26]knowingly used a different route of administration (oral gavage) for the methylmercury hydroxide they administered than the route used for Thimerosal (injection), we *cannot* tell how much of the initial blood-clearance half-life differences those researchers saw in the infant monkeys studied is attributable to the difference in the routes of administration for the two compounds studied.

Furthermore, in studies dating from the 1940s, Engley[32,33] reported that Merthiolate (Thimerosal) and phenylmercury borate had similar toxicities to each other in bacteria, and in studies on human skin and notochord tissue samples.

Therefore, we find that, *instead of the 200-fold safety margin you claim*, the maximum daily dose, "*5 µg/kg/day in a 50-kg person*," is 50 times the EPA's safety level of 0.1 µg/kg/day.

Moreover, if the ophthalmic solutions were given to a child weighing 5 kg, we note that the dose would be 500 times the EPA's 0.1 µg/kg/day.

Based on the preceding considerations, we find that, contrary to your assertion, the use of Thimerosal in ophthalmic products does pose a threat to human health."

"Thimerosal is used in nasal solutions and sprays at concentrations up to 0.002%. Using the dosing regimen previously described (36 actuations/day and 0.07 ml/actuation), the total daily exposure to mercury would be 0.025 mg/day or 0.0005 mg/kg/day, based on a 50-kg person. The NOEL of 1.0 mg/kg/day for chronically administered thimerosal in rats is approximately 2,000 times the estimated exposure to humans based on an exaggerated dose regimen via nasal inhalation. The NOEL is approximately 110 times the estimated exposure in

doi: 10.1588/medver.2007.04.00145

infants (0.009 mg/kg/day, assuming a 3-kg infant) using the same exaggerated dosing regimen. Therefore, we believe that the use of thimerosal in nasal products does not pose a threat to human health.

In general, we agree with your calculation of maximum dose, "*0.025 mg/day or 0.0005 mg/kg/day, based on a 50-kg person*," but are surprised that you did *not* express the daily value in micrograms (0.5 µg/kg/day).

However, we again assert that the EPA's human-derived value (0.1 µg/kg/day), and *not* the rat value, should be used as the safety basis and find that the maximum dose exceed the safe level by a factor of 5 for a 50-kg person and by a factor of 50 for a 5-kg child. [**Note:** Based on the EPA's safe level, this dose would probably only be safe for person who weighed more than 250-kg (551 lb).]

"Thimerosal is used in otic products at a concentration of 0.01% to 0.002%. The maximum concentration is the same as the ophthalmic (0.01%) and the minimum concentration is the same as the nasal products (0.002%). Based on the above assumptions for the nasal and ophthalmic products, we did not perform exposure estimation for the otic products, given that the eye has structures that are more sensitive to topical applications than are those of the ear. Therefore, we believe that the use of thimerosal in otic products does not pose a threat to human health."

Since:

- The EPA's human-based safe level estimate is, if anything, an estimate that has no real 10-fold "safety factor" because a recent study[47] established that the intake of mercury from fish is much lower than the levels estimated by the EPA and, *contrary to the EPA's assumption that the level of mercury in hair were proportional to exposure*, more recent studies[48, 49] were able to show that, *in some of the children tested*, there was no correlation between the two, but
- The EPA's human-based standard for methyl mercury in fish is still a better estimate than the putative NOEL for Thimerosal in studies in rats,

we find that, *as with the other cases you have evaluated*, the maximum exposure levels in all cases, including otic products, clearly exceed the EPA's 0.1 µg/kg/day.

Furthermore, IF that EPA "standard" were corrected for:

- Overestimating the daily intake of methylmercury from fish and
- The invalid assumption that the level of mercury in human hair reflects the level of organic mercury exposure,

THEN the appropriate human NOEL for Thimerosal is probably 0.01 µg/kg/day or lower.

Finally, since a 0.001-ppm level of Thimerosal has been proven to be toxic to growing human neuron system by Parran *et al*.[18] and Thimerosal has been shown to be a bioaccumulate in the brains of developing monkeys as "inorganic mercury" by Burbacher *et al*.,[26] we:

- Understand that Thimerosal is much more toxic than is commonly thought,
- *On that basis*, reject your assessment of its toxicity in humans based on a study in rats, and
- Find that, *based on our current understanding of the toxicity of Thimerosal and the current EPA NOEL for mercury of 0.1 mg/kg/day for mercury from methyl mercury in fish*, all of the current levels of Thimerosal in these products exceed the probably safe levels by factors of 5 to 500 or more.

"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

You state that CoMed's position on mercury is based on the proven harm that ionic mercury causes at levels of approximately 0.02 µg/ml to growing neurological structures when comparable levels of other ionic heavy metals and ionic aluminum have been shown to cause no observable effects (refer to page P-7 of your petition)."

---

47 Gosselin NH, Burnet RC, Carrier G, Bouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data. ***J Expo Anal Environ Epedemiol***. 29 June 2005; **E-pub** (www.nature.com/jea): 1-11.

48 Lyn Redwood, Sallie Bernard, and David Brown, "Predicted Mercury Concentrations in Hair From Infant Immunizations: Cause for Concern," ***NeuroToxicology***, **22**, pages 691-697 (2001).

49 Amy S. Holmes, Mark F. Blaxill and Boyd E. Haley, "Reduced Levels of Mercury in First Baby Haircuts of Autistic Children," ***International Journal of Toxicology***, **22**, pages 277-285 (2003).

doi: 10.1588/medver.2007.04.00145

The **CoMeD** reviewers first notes that you have again failed to state **CoMeD**'s position, which, *when reduced to its basics*, asserts:

You have *knowingly* failed to:

- Comply with federal statutes requiring you to do all that you can to reduce adverse reactions in childhood vaccines that contain any level of Thimerosal or other mercury-based compounds as required by **42 U.S.C. Sec. 300aa-27** since 1987 because Thimerosal has been shown to cause severe adverse reactions, including anaphylaxis at levels down to 10 ppm (0.001%) in vaccine formulations and some childhood vaccines (*e.g.*, some formulations of the inactivated-influenza vaccines that may be given to children).
- Require the manufacturers of vaccines and other drugs that contain preservative levels (defined by you as drug formulations containing these mercury-based compounds at levels between 0.001% and 0.01%) of Thimerosal or other mercury-based drugs are "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" as required by **21 CFR § 610.15(a)** since 1973, a CGMP requirement minimum under **21 CFR § 211.1**, where there this is explicitly required for all biological drug products including vaccines and, **under21 U.S.C. Sec.351(a)(2)(B)** and **21 CFR Part 211**, implicitly required for all drug products.
- Conform to the clear limits imposed on your discretion by the U.S. Supreme court in 1988 by *Berkovitz*.[1]

Nowhere in your response do we find that you have addressed these issues or denied that these issues are applicable to your failure to: **a)** comply with the relevant laws and statutes and/or **b)** ensure that the manufacturers provided the requisite proof of safety for each vaccine formulation or other drug formulation that is preserved with Thimerosal or other mercury-based compound, such as phenylmercuric acetate.

The **CoMeD** reviewers further note that you and the manufacturers of vaccines, *not* the **CoMeD** petitioners, have the burden of proving safety – *a burden you have admitted neither of you have met* – based on scientifically sound and appropriate toxicity studies, using the injection mode of administration, in primates or other animals proven to mimic human response and human sensitivity to mercury poisoning – *not* in oral studies using rats.

Since you have approved using these drugs in pregnant women and Thimerosal is a proven human teratogen, mutagen and carcinogen at levels below 1 ppm, the required studies must include multi-generational reproductive toxicity studies (using test levels 10 times the maximum level of the mercury-containing species in the licensed/approved drug product) along with the appropriate acute (at levels 100 times the highest level in any approved/licensed drug product), chronic (at levels 10 times the highest level in any approved/licensed drug product), long-term "lifetime" studies at the highest dosing level, and in-depth follow-up studies comparing the effect of those inoculated with a controls set who are given a placebo.

As you have admitted, despite having failed to conduct these studies or to require these studies, you have apparently *knowingly* violated the law, *as established by Berkovitz*,[1] by licensing/approving vaccines and other drug products containing preservative levels of Thimerosal or other mercury-based compounds without obtaining the requisite proof of safety.

Based on your actions, it would seem that you are also in the position of knowingly licensing/approving drugs that are adulterated (as *per* **21 U.S.C. Sec. 352(a)(2)(B)**) because they do *not* meet a clear minimum CGMP requirement (as *per* **21 CFR Part 211**, in general, and **21 CFR § 211.1**, in specific) for finished pharmaceutical products.

Further, contrary to your views, we find that all that **CoMeD** did, *in the example you cite*, is offer said example as proof of the reality that inorganic mercury, *which is the known final mercury-containing metabolite of Thimerosal and other mercury-based compounds used as preservatives*, is lethally toxic (harmful) to "*growing neurological structures*" at levels of approximately 0.02 parts per million "*when comparable levels of other ionic heavy metals and ionic aluminum have been shown to cause no observable*" harm – levels that are up to 2,500 times lower than the level of mercury in the typical Thimerosal-preserved biological drug product:

> "**CoMeD**'s position on mercury is based on the proven harm that ionic mercury causes at levels of approximately twenty (20) parts per billion (1,000,000,000) [0.02 ppm; 0.02 µg/mL] to growing neurological structures when comparable levels of other ionic heavy metals (i.e., cadmium, lead, and manganese) and ionic aluminum have been shown to cause no observable harm."**Petition endnote 9** [on page P-7]

"You have cited work done by *Leong, et. al. (2001)*, in support of this statement."

doi: 10.1588/medver.2007.04.00145

We can only agree that **CoMeD** "*cited work done by Leong, et al. (2001), in support of*" **CoMeD**'s position on mercury – namely that inorganic mercury, the ultimate metabolite of Thimerosal in the body, causes harm (is lethally toxic) at levels of approximately 0.02 parts per million to growing neuron structures.

"We note that these investigators used an in vitro cell culture system consisting of neuronal cells from a snail to evaluate the effect of chloride salts of mercury, lead, cadmium, and manganese (1×10^{-7M}) on neurite growth cone morphology and behavior. Snail cells were treated with heavy metal solutions by applying pressure injection into the culture media adjacent to neuronal growth cones of the snail. Results showed that mercury ions, when directly infused into in vitro cultures of nerve cells from an invertebrate, inhibit growth of neuronal structures. FDA acknowledges these data;"

Though we are glad you acknowledge these data, we note that you have misstated the paper's findings because the authors found that mercury did more than your "*inhibit growth of neuronal structures*," it was lethal to the growing neurites and the neurons themselves.

"however, the data do not prove that thimerosal in vaccines causes autism in humans,"

Since:

- The **CoMeD** petitioners did *not* offer this example as proof that Thimerosal in vaccines causes autism in humans, and
- Autism is, by definition a "causeless disorder" diagnosed by symptoms exhibited and *not* by causal factors,

the **CoMeD** reviewers find that this remark is, *at best*, inappropriate here.

"and the investigators did not even attempt to establish that those data are in any way relevant to determining whether any causal relationship exists between thimerosal in vaccines and the development of autism in humans."

The **CoMeD** reviewers find your remarks here even more curious and non-relevant because, *as you quote in your next statement*, this example is offered as evidence that Thimerosal's ultimate metabolite in human brains, inorganic mercury, causes neurological damage.

What the investigators in this example did, or did *not*, attempt to do is *not* relevant – only their valid findings, which you do *not* dispute, are relevant.

Furthermore, on page P-2 in your petition you state that "there is substantial inferential evidence, and some Thimerosal and related-compounds human exposure and animal data that have **proven** Thimerosal and other mercury-based compounds can cause neurological damage in susceptible individuals at levels of exposure above 0.1 microgram (µg) of mercury per kg."

First, the **CoMeD** reviewers note that you have misquoted the petition by changing the **bolding** in it to only emphasize the word "***proven***" when the **bolding** actually encompasses most of the statement:

" … **there is substantial inferential evidence, and some Thimerosal and related-compounds human exposure and animal data, that have proven Thimerosal and other mercury-based compounds can cause neurological damage in *susceptible* individuals** at levels of exposure **above** 0.1 microgram (µg) of mercury per kilogram (kg).[6]"

Second, we note that you have quoted a portion of a note to an issue without including its context – an action we find that distorts the remark.

Properly, *in context*, the **CoMeD** citizen petition states (with underlining added to highlight the portion of the "**Note**" you chose to quote) [**see** petition's page P-2]:

"**2.** *Until the federal government can **establish** that any and all Thimerosal-containing products have no less than a **10X** safety margin with respect to the risk of causing any level of neurological damage to developing fetuses, newborns, children and adolescents*, we request that the Commissioner of the Food and Drug Administration move to withdraw the approval (under **21 U.S.C. 355(e)**) of any FDA-approved drug product (*e.g.*, ophthalmic products) and revoke the license (under **42 U.S.C. 262(a)(2)(A))** of any FDA-licensed biological product (*e.g.*, vaccines and other preserved serological preparations) that uses Thimerosal, *or any other mercury-based neurotoxic compound*, as a 'preservative' or 'adjuvant' unless the federal government and/or the manufacturer of said medical product can **prove, at its maximum level, its safety and efficacy as a preservative or adjuvant** in scientifically sound animal model studies using appropriate susceptible animal strains as the test subjects. [**Note:** We make this request because, *as all*

doi: 10.1588/medver.2007.04.00145

parties (federal government, industry, academia, and the public) know" **petition endnotes 3,4** "**, all such current products lack the appropriate safety studies.** *Despite the recent* report" **petition endnote 5** "*by the Institute of Medicine (IOM)*, **there is substantial inferential evidence, and some Thimerosal and related-compounds human exposure and animal data, that have proven Thimerosal and other mercury-based compounds can cause neurological damage in *susceptible* individuals** at levels of exposure **above** 0.1 microgram (µg) of mercury per kilogram (kg)" **petition endnote 6** "*. For the other recognized hazardous alkyl mercury compound, methyl mercury*, the current EPA (United States Environmental Protection Agency) guideline" **petition endnote 7** "for methyl mercury from all sources for 'infants' is *not more than* 0.1 µg/kg/day (0.093 µg of mercury/kg/day).]"

Otherwise, the **CoMeD** reviewers do *not* disagree with your statement here.

"You state further that, 'scientifically sound experimental studies have proven the neurotoxicity of Thimerosal and its metabolites, ethyl mercury and mercuric ion, at 'mercury' levels below 0.1 part-in-a-million (0.1 ppm; 0.1 µg per mL or g)' (page P-11 of your petition). You have cited endnote 6 in support of these statements, i.e., studies performed by *Baskin. et al. (2003)*, *Makani, et al. (2002)*, *Waly, et al, (2004)*, *Chao, et al. (1984)*, and *Leong, et al. (2001)*."

First, the **CoMeD** reviewers note that you have again misquoted the petition here by leaving out the bolding and the underlining emphases because the **CoMeD** citizen petition actually states:

- "**Scientifically sound experimental studies have proven** the **neurotoxicity** of Thimerosal and its metabolites, ethyl mercury and mercuric ion, **at "mercury" levels below 0.1 part-in-a-million** (0.1 ppm; 0.1 µg per mL or g) …" [**See** petition's page P-11.]

Thus, we find that it is clear that the issue raised by **CoMeD** was neurotoxicity caused by "Thimerosal and its metabolites, ethyl mercury and mercuric ion" – in other words, mercury-poisoning of neuron structures – "**at 'mercury' levels below 0.1 part-in-a-million**" and *not*, as you have asserted earlier, issues such as "autism" or what causes this supposedly causeless neurological disorder.

"These studies were carried out using in vitro cell culture based assays of human cerebral neurons, human T-cell lines, human cervical carcinoma cell lines, and human neuroblastoma cells to evaluate the effects of thimerosal or mercury compounds on cellular processes and pathways, including programmed cell-death (apoptosis), DNA and RNA replication and methylation pathways. Results from these in vitro studies show that mercurial compounds, when directly applied to cell cultures can exert dose-dependent toxic effects."

In general, the **CoMeD** reviewers agree with your representation here.

However, we object to your failure to state that these effects include cell death and non-reversibly damage that destroys neurons and the synaptic linkages between neurons.

"FDA acknowledges these data but concludes that these studies do not prove that thimerosal contributes to the risk of autism for the following reasons: The biochemical and molecular pathways and processes relevant to the expressions of autism are currently not known. Therefore, there is no basis for concluding that the biochemical and molecular pathways studied in these in vitro cell systems are related to the biological processes that underlie the disease of autism."

First, we are heartened to see that, by stating the "*FDA acknowledges these*," the FDA is implicitly acknowledging that they are valid data.

However, since the issues the **CoMeD** citizen petition raises are *not* dependent on whether or not "*these studies do not prove that thimerosal contributes to the risk of autism*," because autism *per se* is *not* an underlying issue in this petition.

Thus, we find that your response *inappropriately* considers the issue of Thimerosal causing autism but does *not*, as it should, consider the potential for Thimerosal and other mercurials in pharmaceuticals to cause mercury poisoning, *which is an underlying issue in the* **CoMeD** *petition*, to the degree that: **a)** this poisoning affects different cells, tissues, organs, and biological pathways in the body and **b)** those persons affected plainly manifest one or more of the clinical symptoms of mercury poisoning.

Therefore, we suggest that you and any subsequent reviewer of our assessment of this petition simply ignore your remarks here because they are *not* germane to the underlying issues raised by **CoMeD** in this petition.

"Furthermore, in some of the studies you cite, the effects observed were not specific to mercury compounds, but were also noted with ethanol, lead, and aluminum (e.g., *Waly. et al., 2001*)."

doi: 10.1588/medver.2007.04.00145

Since you do *not* dispute that the studies **CoMeD** cited address the toxicity of mercury, we again suggest that your non-germane statement here should simply be ignored.

"The thrust of your argument appears to be that thimerosal and its metabolites were studied in these in vitro systems using dose levels in the same range, or even lower, than those contained as trace amounts in some of the currently recommended childhood vaccines. FDA acknowledges and values the importance of in vitro systems to elucidate possible mechanisms for drug-induced effects."

We are heartened that the "*FDA acknowledges and values the importance of in vitro systems to elucidate possible mechanisms for drug-induced effects*."

"However, demonstration of a toxic effect of a compound in an in vitro system using isolated cells does not readily translate into potential toxic effects to the human body. The studies you cite assessed the effects of thimerosal and its metabolites on cellular pathways under conditions of in vitro exposure that were extreme in terms of dose regimen, duration, and method of administration. Furthermore, some of the studies required extensive manipulation of the cell system, e.g., heavy metal solutions were delivered via pressure injection into snail neuronal cell culture media for a duration of 20 minutes. However, such exposure may not be achieved in vivo, since in the context of a whole organism, it would depend on the uptake (e.g., absorption), distribution, metabolism, and excretion pathways of the compound. Therefore, the dose levels of thimerosal and its metabolites studied in these in vitro systems may not model the actual cellular levels of exposure in the context of the human body."

First, we simply reject your unsubstantiated statements concerning the utility and applicability of the "*toxic effect of a compound in an in vitro system using isolated cells does not readily translate into potential toxic effects to the human body*."

In addition, we find that you failed to provide any proof of safety for the drug products in question or a scientific basis for the dismissing any or all the studies referenced.

Second, your response inappropriately addresses the tangential issue of Thimerosal's causing autism, *an issue recognized by Congress in 2003*,[7] but fails to address one of the underlying petition issues – the potential for Thimerosal and other mercurials in pharmaceuticals to cause mercury poisoning that may affect different cells, tissues, organs, and biological pathways in the body to the degree that this poisoning manifests as one or more of the recognized symptoms of clinical mercury poisoning.

With respect to your, "*The studies you cite assessed the effects of thimerosal and its metabolites on cellular pathways under conditions of in vitro exposure that were extreme in terms of dose regimen, duration, and method of administration*," we find that, *in general*, the conditions used were *not* "extreme" but rather typical of those conditions used in such *in vitro* toxicity assessment studies.

For example, in acute toxicity studies, the levels administered are, *for obvious reasons*, overdoses – else how would a LD50 be determined?

Thus, we find that you are either naive about the design and execution of *in vitro* toxicity studies or, *more likely*, attempting to mislead the reader with unsubstantiated rhetoric concerning the nature of *in vitro* toxicity evaluation and its applicability to humans or other animals.

"It is generally accepted that drug-induced toxicity depends on the conditions of a drug's use, such as dose, route, regimen, and duration of treatment. For example, acetaminophen (Tylenol) is a commonly used painkiller for mild to moderate pain and is considered safe and effective when administered according to the recommended doses. However, if taken in overdose, acetaminophen causes liver failure. Furthermore, when studied in in vitro cultures of isolated cells, it can cause a dose-dependent toxicity leading to cell injury and cell death (*Pierce. et al., 2002, Biochem. Pharmacol. 64:413-24, Bajt, et al., 2004, Toxicological Sciences 80:343-349*)."

First, we agree, "*drug-induced toxicity depends on the conditions of a drug's use, such as dose, route, regimen, and duration of treatment.*"

However, the Tylenol example is *not* germane to the issue of toxicology studies and, though it "*is considered safe and effective when administered according to the recommended doses*," there are documented cases of liver toxicity in persons who have adhered to the prescribing instructions but have developed liver toxicity because they are more "susceptible" to the adverse effects of Tylenol.

Moreover, in making your statement, "*Furthermore, when studied in in vitro cultures of isolated cells, it can cause a dose-dependent toxicity leading to cell injury and cell death*," you have failed to establish any linkage between the reported

doi: 10.1588/medver.2007.04.00145

behavior of Tylenol, *typically taken at does of 200 mg to 800 mg or higher*, and Thimerosal and related mercury-based preservatives administered at levels of 0.05 mg to 0.005 mg.

Further, in cases where a compound is acutely toxic, like Thimerosal and the other mercury-based compounds used as preservatives, the toxicology data collected clearly indicate that there is a dose-time dependence between Thimerosal or the other mercury-based compounds and any of the effects that Thimerosal or other mercury-based compounds have been found to exhibit in both *in vitro* and *in vivo* studies.

At low enough levels, the harmful effects can, *in many cases*, be reversed or blocked by other compounds without damage to the cellular system, tissue or body being studied.

Since the current issues revolve around finding the true level at which Thimerosal or any other mercury-based compound will have no significant adverse effect or be sufficiently nontoxic at the dosing level, the facts for Thimerosal appear to be that the current lowest level at which no toxic effect will be seen in any human neural cell system maintained without external detoxification systems is somewhere below 0.001 ppm Thimerosal, 0.0005 ppm mercury, for apoptotic injury and death, provided both the test and the control system can be maintained in a nominally viable state for more than 2 days.

Given the preceding realities, rather than attempting to raise tangential issues (like autism, Tylenol, pathway, and dose), we find that you should be focusing what you are *not* doing –

- Proving or, *more accurately*, having the drug manufacturers prove what the truly "sufficiently nontoxic" level, *if any*, is for Thimerosal and other mercury-based compounds used as a preservative in pharmaceutical vaccine or other biological drug product or manufacturing process because the law (**21 CFR § 610.15(a)**) requires that this be done and
- Reducing the risk of adverse reactions in Thimerosal-containing childhood vaccines as explicitly required by **42 U.S.C. Sec. 300aa-27(a)(2)** because Thimerosal has been proven to cause severe adverse reactions including anaphylaxis and death at Thimerosal levels down to 10 ppm and some current childhood vaccines (*e.g.*, the Thimerosal-preserved influenza vaccines, which are allowed to be given to children, may contain Thimerosal levels of up to "120 ppm" in individual doses).

"FDA concludes that the data derived from the in vitro cell-based assays that you cite do not provide proof that thimerosal contained in the medical products and used under conditions described in labeling causes neurological damage in susceptible individuals and/or may contribute to the risk of autism."

The **CoMeD** reviewers must reject your conclusion because you: **a)** have failed to prove or **b)**, *as required by law*, have the manufacturers prove that the level of Thimerosal in Thimerosal-preserved vaccines or other biological drug products meet the safety minimums set forth in **21 CFR § 610.15(a)** for preservatives (or, *implicitly*, have the manufacturers of other drugs) prove the level of Thimerosal or other mercury-based compound used as a preservative in any drug is "sufficiently nontoxic."

We find that you are attempting to avoid the legal reality that the burden of proving safety at the minimums established in the regulations is the non-dischargeable absolute duty that the vaccine makers and other drug manufacturers have to meet and that, under *Berkovitz*,[1] you have no discretion to approve/license any drug product that fails to meet a clear policy, law or statute, including but not limited to **21 CFR § 610.15(a)** explicitly for preservatives in biological drug products and **21 U.S.C. Sec. 351(a)(2)(B)** implicitly for all drugs, that contains a requirement minimum that must be met before approval or licensing can be granted or legally continued.

In addition, we find that you have *knowingly* failed to meet the statutory mandate set forth in **42 U.S.C. Sec 300aa-27(a)(2)** to reduce the adverse reactions in all childhood vaccines

Finally, we note that, *since the Congress of the United States of America has determined*[7] *that there is a probable connection between Thimerosal in vaccines and autism*, you should take this issue up with Congress.

This is the case because Congress, and *not* the **CoMeD** petitioners, determined that this link existed in May of 2003, more than a year before the **CoMeD** citizen petition was submitted to the FDA for consideration in August 2004 as the **CoMeD** petitioners clearly stated in their petition (**see** pages P-17 and P-18):

> " The Food and Drug Administration's (FDA) mission is to 'promote and protect the public health by helping safe and effective products reach the market in a timely way, and monitoring products for continued safety after they are in use.' However, the FDA uses a subjective barometer in determining when a product that has known risks can remain on the market. According to the agency, 'at the heart of all FDA's product evaluation

doi: 10.1588/medver.2007.04.00145

> decisions is a judgment about whether a new product's benefits to users will outweigh its risks. No regulated product is totally risk-free, so these judgments are important. FDA will allow a product to present more of risk when its potential benefit is great—especially for products used to treat serious, life-threatening conditions.' This argument—that known risks of infectious diseases outweigh a potential risk of neurological damage from exposure to thimerosal in vaccines-is one that has continuously been presented to the Committee by government officials. FDA officials have stressed that any possible risk from thimerosal was theoretical: that no proof of harm existed. However, the Committee, upon a thorough review of the scientific literature and internal documents from government and industry, did find evidence that thimerosal did pose a risk. …
> …
> … Thimerosal used as a preservative in vaccines is likely related to the autism epidemic. This epidemic in all probability may have been prevented or curtailed had the FDA not been asleep at the switch regarding the lack of safety data regarding injected thimerosal and the sharp rise of infant exposure to this known neurotoxin. Our public health agencies' failure to act is indicative of institutional malfeasance for self-protection and misplaced protectionism of the pharmaceutical industry."[50]

Finally, we note that the FDA's claimed administrative discretion, "at the heart of all FDA's product evaluation decisions is a judgment about whether a new product's benefits to users will outweigh its risks," has been limited by the U.S. Supreme Court in a unanimous 1988 decision, *Berkovitz*,[1] which *clearly* requires that a manufacturer must meet all applicable legally policies, laws and statutes before the FDA can legally exercise its administrative discretion to license/approve any drug product.

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

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

You cite studies by *Hornig, et al.* (endnote 59), and *Havarinasab, et al.* (endnote 60), conducted in genetically susceptible rodent models, presumably to support the hypothesis that 'damaged children are members of a genetically vulnerable, mercury-sensitive subpopulation' (refer to pages P-40, P-42, P-43, and P-44 of your petition)."

First, we note

- You have taken these studies out of the context in which they were presented and
- By so doing, you have distorted the reasons they were cited and their importance to the petition.

Thus, before proceeding to discuss these articles, we need to reestablish their context.

Factually, the cited articles fall under the umbrella of toxicology studies presented to address:

"**8. *The Link Between Thimerosal And Neurological Disorders***."

as a part of the body of existing:

"***10. Clinical Evidence***.

Specifically, the cited studies are part of "**11. *Significant 2004 Studies***" cited, *as the outline suggests*, in support of the link between Thimerosal and neurological disorders that they **CoMeD** petitioners has established have a significant mercury poisoning component.

In that regard, we note that these studies were put-forward principally to show that the administration of Thimerosal at doses comparable to those received from vaccines or other pharmaceutical-containing products, or at doses several-fold higher, have been demonstrated to cause toxicity (damage) in animal models (*i.e*. proof that administering low levels of Thimerosal [49.55% mercury by weight] causes mercury poisoning in animal models or, simplistically, administering mercury causes mercury poisoning – a straightforward proposition).

Thus, the cited animal model studies show mercury toxicity following administration of Thimerosal to animal model systems mimicking potential human exposures to Thimerosal from pharmaceutical products.

---

[50] Subcommittee on Human Rights and Wellness, Committee on Government Reform of the House of Representatives, "*Mercury in Medicine Report*," Washington, DC, as published in the ***Congressional Record***, pgs. E1011-E1030, May 21, 2003.

doi: 10.1588/medver.2007.04.00145

Once again, the **CoMeD** reviewers find you are attempting to dismiss these studies without providing a scientific rationale to justify your dismissal of these studies with respect to their showing mercury toxicity in animals following Thimerosal administration – the issue the **CoMeD** petitioners are addressing in this part of the **CoMeD** citizen petition.

"*Havarinasab, et al.* studied whether thimerosal induces a systemic autoimmune condition that can be observed in genetically susceptible mice exposed to inorganic mercury. The authors state that using the dose-response data in mice, genetically susceptible humans would need to absorb at least 147 µg mercury/kg per day for at least 5 days to develop autoimmunity. Based on conservative calculations considering the cumulative dose of mercury from thimerosal in vaccines that infants would have been exposed to **prior** to 1999, the authors conclude that **'there exists no significant risk for de novo induction of systemic autoimmunity in humans due to thimerosal in vaccines.'**"

Before addressing your comments, the **CoMeD** reviewers must note that, with respect to this study, the petition stated (with underlining added to highlight the important issues addressed):

"Also, in **2004**, Havarinasab et al.[Petition endnote 60] reported that Thimerosal, *which was primarily present in the tissues as ethyl mercury and ionic mercury*, has caused illness and several deaths due to erroneous handling when used as a disinfectant or as a preservative in medical preparations. [**See** petition's page P-43.]

The authors stated:

'We have studied if thimerosal might induce the systemic autoimmune condition observed in genetically susceptible mice after exposure to inorganic mercury. A.SW mice were exposed to 1.25-40 mg thimerosal/l drinking water for 70 days. Antinucleolar antibodies, targeting the 34-kDa protein fibrillarin, developed in a dose-related pattern and first appeared after 10 days in the two highest dose groups. The lowest observed adverse effect level (LOAEL) for antifibrillarin antibodies was 2.5 mg thimerosal/l, corresponding to an absorbed dose of 147 microg Hg/kg bw and a concentration of 21 and 1.9 microg Hg/g in the kidney and lymph nodes, respectively. The same LOAEL was found for tissue immune-complex deposits. The total serum concentration of IgE, IgG1, and IgG2a showed a significant dose-related increase in thimerosal-treated mice, with a LOAEL of 5 mg thimerosal/l for IgG1 and IgE, and 20 mg thimerosal/l for IgG2a. The polyclonal B-cell activation showed a significant dose-response relationship with a LOAEL of 10 mg thimerosal/l. Therefore, thimerosal induces in genetically susceptible mice a systemic autoimmune syndrome very similar to that seen after treatment with inorganic mercury, although a higher absorbed dose of Hg is needed using thimerosal. The autoimmune syndrome induced by thimerosal is different from the weaker and more restricted autoimmune reaction observed after treatment with an equipotent dose of methyl mercury.'" [**See** petition pages P-43 and P-44.]

Though your letter states, "*Havarinasab, et al. studied whether thimerosal induces a systemic autoimmune condition that can be observed in genetically susceptible mice exposed to inorganic mercury*," you failed to note that the researchers did indeed find "thimerosal induces in genetically susceptible mice a systemic autoimmune syndrome very similar to that seen after treatment with inorganic mercury" (petition endnote 60).

With respect to your "*The authors state that using the dose-response data in mice, genetically susceptible humans would need to absorb at least 147 µg mercury/kg per day for at least 5 days to develop autoimmunity*," we find that, the researchers assumption that humans respond with the same insensitivity to mercury as mice is *not* supported by any evidence that these researchers or you present.

Furthermore, *returning to the PMA discussion*, you will note that the EPA, *understanding the fundamental differences between chemical sensitivity to organic mercury compounds in rodents and humans*, converted the observed 8.4 µg/kg/day NOEL for daily PMA intake in rats into a 0.08 µg/kg/day ADI for humans – effectively dividing the $NOEL_{rat}$ by 100 to estimate the ADI_{human}.

Based on this reality, these researchers should have divided the observed LOAEL "*for antifibrillarin antibodies*" (2.5 mg thimerosal/l [2.5 ppm Thimerosal]) and "*the absorbed dose*" ("*147 microg Hg/kg bw*") by 100 and estimated the human "*absorbed dose*" needed to trigger autoimmune response as 1.47 µg Thimerosal/kg.

Based on this human-appropriate "*absorbed dose*" and a single 0.25-mL dose (the dose given to young children) of a vaccine preserved with 0.01% Thimerosal, *as most were and some still are*, could exceed the autoimmune triggering threshold for humans when the child injected weighs less than 17 kg (37.7 lb) because a 0.25-mL dose nominally delivers 25 µg of Thimerosal.

Similarly, *for older children and adults*, where the dose is 50 µg (0.5 mL of Thimerosal-preserved vaccine), a single does could exceed the autoimmune triggering threshold when the person injected weighs less than 34 kg (75 lb).

doi: 10.1588/medver.2007.04.00145

Since, *as you admit*, the statement you quoted, "***there exists no significant risk for de novo induction of systemic autoimmunity in humans due to thimerosal in vaccines***"

- Is based on an invalid assumption that "*using the dose-response data in mice*" is appropriate for humans and
- At odds with the researchers' admission that Thimerosal is actually known to cause "acrodynia" and "is a well-known sensitizing agent":

  "Thimerosal is a well-known sensitizing agent, although usually of no clinical relevance. In rare cases, thimerosal has caused systemic immune reactions including acrodynia,"

which supports the reality that Thimerosal does and has actually mercury-poisoned humans to the point that they exhibit acrodynia[51] – which is a known form of clinical mercury poisoning.

Thus, we find that your representation of these researchers' paper does *not* negate the purpose for which the petitioners included it – clear evidence that administering Thimerosal causes mercury poisoning.

"*Hornig, et al.* exposed mice pups of different genetic backgrounds (SJL/J, C57 BL/6J and Balb/cJ) to thimerosal in dose and timing equivalent to the pediatric immunization schedule of 2001. The authors state that genes linked to autoimmunity in general, and to mercury-induced autoimmunity in particular, may influence the relative neuro-or immunotoxicity of thimerosal, thus highlighting the importance of interactions of gene, environment, and timing in the pathogenesis of neurodevelopmental disorders."

We agree with you that:

- "*Hornig, et al. exposed mice pups of different genetic backgrounds (SJL/J, C57 BL/6J and Balb/cJ) to thimerosal in dose and timing equivalent to the pediatric immunization schedule of 2001*," and
- "*The authors state that genes linked to autoimmunity in general, and to mercury-induced autoimmunity in particular, may influence the relative neuro-or immunotoxicity of thimerosal, thus highlighting the importance of interactions of gene, environment, and timing in the pathogenesis of neurodevelopmental disorders*."

"The studies cited using genetically susceptible rodent models assume that autism is caused by an autoimmune reaction."

First, *upon again reviewing Hornig et al*., we find that your statement here mischaracterizes the researchers work by substituting "*assume*" for "hypothesize."

As the researchers stated in the paper's abstract (with underlining added to highlight the issue at hand):

"The developing brain is uniquely susceptible to the neurotoxic hazard posed by mercurials. Host differences in maturation, metabolism, nutrition, sex, and autoimmunity influence outcomes. How population-based variability affects the safety of the ethylmercury-containing vaccine preservative, thimerosal, is unknown. Reported increases in the prevalence of autism, a highly heritable neuropsychiatric condition, are intensifying public focus on environmental exposures such as thimerosal. Immune profiles and family history in autism are frequently consistent with autoimmunity. We hypothesized that autoimmune propensity influences outcomes in mice following thimerosal challenges that mimic routine childhood immunizations, …" (petition's endnote 59),

which clearly indicates that they made no assumptions, but were rather trying, *as scientists do*, to test a ***working hypothesis***.[52]

As these researchers clearly stated, their ***working hypothesis*** was that "autoimmune propensity influences outcomes in mice following thimerosal challenges" and what they were attempting to study was the "neurotoxic hazard posed by mercurials" – in this case the "neurotoxic hazard posed by" Thimerosal using strains of mice with "autoimmune propensity" as the test subjects and mice without "autoimmune propensity" as controls.

Thus, your "*assume that autism is caused by an autoimmune reaction.*" is a *knowing* misrepresentation of the facts relating to this study.

---

[51] **Merriam-Webster's Medical Dictionary**, 1995, page 8, defines "**ac·ro·dyn·ia**" as "a disease of infants and young children that is an allergic reaction to mercury, is characterized by dusty pink discoloration of hands and with local swelling and intense itching, and is accompanied by insomnia, irritability, and sensitivity to light **—** called also *erythredema*, *pink disease*, *Swift's disease*"

[52] Webster's New Universal Unabridged Dictionary, 2001, page 945, column 1, "**hy·poth·e·sis**" is primarily defined as "a proposition, or set of propositions, set forth as an explanation for the occurrence of some specified group of phenomena, either asserted merely as a provisional conjecture to guide investigation (**working hypothesis**) or accepted as highly probable in the light of the established facts."

doi: 10.1588/medver.2007.04.00145

As the title of their paper, "Neurotoxic effects of postnatal thimerosal …" clearly indicates, they were studying "the neurotoxic hazard posed by mercurials" to the "developing brain," and *not* your fabricated "*autism is caused by an autoimmune reaction*."

"However, there is no evidence that autistic patients have auto-immune-mediated central nervous system (CM) damage in the brain (see 2004 IOM Report) and there is currently limited understanding of the etiology of autism."

Since the cited paper is *not* based on any assumption that "*autistic patients have auto-immune-mediated central nervous system (CM) damage in the brain*," your statement here is apparently a knowing attempt on your part to further mislead any reader of your letter and, *as such*, is scientifically and legally reprehensible.

Based on the preceding facts, we find that your statement adds nothing to the facts that this research paper established.

Factually, we confirm the **CoMeD** petitioners reported the important findings and the citizen petition reflected the researchers' work as follows (with underlining added to highlight the underlying issues (petition pages P-42 & P-43):

" Most recently, Mady Hornig *et al*.[petition endnote 59] **reported** (in June of 2004) that, *following exposure to Thimerosal reflecting the United States' childhood immunization schedule (i.e., the dose and stage of development)*, **autoimmune disease-sensitive SJL/J mice developed symptoms mirroring childhood autism, including:**

- ✓ Growth delay;
- ✓ Reduced locomotion;
- ✓ Decreased numbers of Purkinje cells;
- ✓ Exaggerated response to novelty;
- ✓ Significant abnormalities in brain architecture, affecting areas subserving emotion and cognition; and
- ✓ Densely packed, hyperchromic hippocampal neurons with altered glutamate receptors and transporters.

However, the same treatment regimen did **not** similarly affect two mouse strains, C57BL/6J and BALB/cJ, that are not autoimmune sensitive.

The authors concluded that their findings:

a. Support the hypothesis that the adverse outcomes observed have **a genetic component**, **and**
b. Provide a model for investigating Thimerosal-related neurotoxicity."

Thus, the importance of their work is that they able to duplicate the symptoms and altered brain structures found when developing children are mercury poisoned by dosing neonatal SJL/J mice with Thimerosal under conditions mimicking those experienced by a developing human child inoculated in a manner paralleling the recommended U.S. 2001 childhood immunization schedule – thus proving that using Thimerosal-preserved vaccines does poison newborns who, *for whatever reasons*, are "susceptible" to being mercury poisoned, since the other two strains of mice tested were *not* susceptible to being mercury poisoned under this Thimerosal-toxicity-assessment protocol.

Therefore, their work provided evidence that Thimerosal-preserved vaccines can cause brain damage mimicking many of the symptoms, behaviors, and/or brain-structure abnormalities seen in children diagnosed with severe neurodevelopmental disorders.

Thus, their work:

- Established Thimerosal-preserved vaccines represent a mercury-poisoning risk to some neonates but not others, and
- Identified an animal model, SJL/J mice, that can be used to study the toxicity of Thimerosal at low levels in individuals that are known to be susceptible to mercury poisoning.

"Therefore, FDA concludes and agrees with the IOM that even though these rodent models are useful for understanding some of the processes by which exogenous agents may potentially exert adverse effects, the connection between these models and autism is only theoretical (see 2004 IOM report)."

Since this study was clearly *not* designed to connect "*these models and autism*," your statement here should be ignored because it not only supports your views of an IOM position, but also *neither* addresses the findings in the Hornig paper *nor* challenges the validity of the Thimerosal toxicity findings published therein.

doi: 10.1588/medver.2007.04.00145

"FDA wishes to comment on your statement on page P-2, namely that the safety and efficacy of thimerosal, or any other mercury-based compound, be studied in scientifically sound animal studies using appropriate susceptible animal strains. Prior to introducing a novel vaccine formulation into clinical trials, the vaccine is evaluated in nonclinical studies using animal models to assess and detect the potential of the product to cause harm in the animal."

Given your admitted refusal to enforce the law and require manufactures to provide proof that their Thimerosal-preserved vaccines meet the clear requirement set forth in **21 CFR § 610.15(a)** that the "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," the **CoMeD** reviewers are, at best, bemused by your comment here.

We therefore again ask you to enforce this clear requirement on all preserved biological products including biological products preserved with Thimerosal or other mercury-based compounds as a preservative.

Moreover, though your, "*Prior to introducing a novel vaccine formulation into clinical trials, the vaccine is evaluated in nonclinical studies using animal models to assess and detect the potential of the product to cause harm in the animal*," statement seemingly admits that animal models are valid for evaluating the toxicity of Thimerosal in vaccines, when studies presented in the **CoMeD** petition clearly showed toxicity from Thimerosal in animals, you seem to have decided not only to give them no weight but also to address issues of your own creation rather than address the clear evidence of Thimerosal toxicity presented by the **CoMeD** petitioners here.

Since the **CoMeD** reviewers understand the importance of providing more evidence of Thimerosal toxicity in animal studies, we are including the citations for, *and abstracts of*, three additional published studies, *including two that were published after* **CoMeD** *filed their citizen petition*, that have evaluated the toxicity of Thimerosal in animal model systems, including studies that have evaluated the toxicity of Thimerosal at doses within the range that individual Americans may be administered:

1. Uchida T, Naito S, Kato H, Hatano I, Harashima A, Terada Y, Ohkawa T, Chino F, Eto K. Thimerosal induces toxic reaction in non-sensitized animals. ***Int Arch Allergy Immunol***. 1994 Dec; **105**(4): 408.

   "The effects of injection of thimerosal solution on nonsensitized animals was investigated. Intrafootpad injection of thimerosal solution in nonsensitized mice resulted in a swelling response which peaked 1 h after injection and lasted for more than 24 h. Histopathological examination showed that there were severe edema and infiltration of polymorphonuclear neutrophils at the site of injection. An increased vascular permeability was observed after cutaneous injection of thimerosal solution on the back of nonsensitized rats. Since mercuric chloride and methyl mercury induced severer reactions, and thiosalicylic acid had no effect, mercury contained in thimerosal would have caused the reactions observed in this study. These results suggest that part of these hypersensitivity reactions against thimerosal observed among patients were possibly induced by the toxic effect of thimerosal. Therefore, thimerosal contained as a preservative in vaccine may augment the side-effects of the vaccination."

2. Havarinasab S, Haggqvist B, Bjorn E, Pollard KM, Hultman P. Immunosuppressive and autoimmune effects of thimerosal in mice. ***Toxicol Appl Pharmacol***. 2005 Apr 15; **204**(2):109-121.

   "The possible health effects of the organic mercury compound thimerosal (ethylmercurithio-salicylate), which is rapidly metabolized to ethylmercury (EtHg), have recently been much debated and the effect of this compound on the immune system is largely unknown. We therefore studied the effect of thimerosal by treating A.SW (H-2s) mice, susceptible to induction of autoimmunity by heavy metals, with 10 mg thimerosal/L drinking water (internal dose ca 590 microg Hg/kg body weight/day) for up to 30 days. The lymph node expression of IL-2 and IL-15 mRNA was increased after 2 days, and of IL-4 and IFN-gamma mRNA after 6 and 14 days. During the first 14 days treatment, the number of splenocytes, including T and B cells as well as Ig-secreting cells decreased. A strong immunostimulation superseded after 30 days treatment with increase in splenic weight, number of splenocytes including T and B cells and Ig-secreting cells, and Th2- as well as Th-1-dependent serum immunoglobulins. Antinucleolar antibodies (ANoA) targeting the 34-kDa nucleolar protein fibrillarin, and systemic immune-complex deposits developed. The H-2s strains SJL and B10.S also responded to thimerosal treatment with ANoA. The A.TL and B10.TL strain, sharing background genes with the A.SW and B10.S strain, respectively, but with a different H-2 haplotype (t1), did not develop ANoA, linking the susceptibility to H-2. Thimerosal-treated H-2s mice homozygous for the nu mutation (SJL-nu/nu), or lacking the T-cell co-stimulatory molecule CD28 (B10.S-CD28-/-), did not develop ANoA, which showed that the autoimmune response is T-cell dependent. Using H-2s strains with targeted mutations, we found that IFN-gamma and IL-6, but not IL-4, is important for induction of ANoA by thimerosal. The maximum added renal concentration of thimerosal (EtHg) and inorganic mercury occurred after 14 days treatment and was 81 microg Hg/g. EtHg made up 59% and inorganic mercury 41% of the

doi: 10.1588/medver.2007.04.00145

renal mercury. In conclusion, the organic mercury compound thimerosal (EtHg) has initial immunosuppressive effects similar to those of MeHg. However, in contrast to MeHg, thimerosal treatment leads in genetically susceptible mice to a second phase with strong immunostimulation and autoimmunity, which is T-cell dependent, H-2 linked and may at least partly be due to the inorganic mercury derived from the metabolism of ethyl mercury."

3. Havarinasab S, Hultman P. Alteration of the spontaneous systemic autoimmune disease in (NZB x NZW)F1 mice by treatment with thimerosal (ethyl mercury). ***Toxicol Appl Pharmacol***. 2006 Jul 1; **214**(1): 43-54.

"Inorganic mercury may aggravate murine systemic autoimmune diseases which are either spontaneous (genetically determined) or induced by non-genetic mechanisms. Organic mercury species, the dominating form of mercury exposure in the human population, have not been examined in this respect. Therefore, ethyl mercury in the form of thimerosal, a preservative recently debated as a possible health hazard when present in vaccines, was administered in a dose of 0.156-5 mg/L drinking water to female (NZB x NZW)F1 (ZBWF1) mice. These mice develop an age-dependent spontaneous systemic autoimmune disease with high mortality primarily due to immune-complex (IC) glomerulonephritis. Five mg thimerosal/L drinking water (295 microg Hg/kg body weight (bw)/day) for 7 weeks induced glomerular, mesangial and systemic vessel wall IC deposits and antinuclear antibodies (ANA) which were not present in the untreated controls. After 22-25 weeks, the higher doses of thimerosal had shifted the localization of the spontaneously developing renal glomerular IC deposits from the capillary wall position seen in controls to the mesangium. The altered localization was associated with less severe histological kidney damage, less proteinuria, and reduced mortality. The effect was dose-dependent, lower doses having no effect compared with the untreated controls. A different effect of thimerosal treatment was induction of renal and splenic vessel walls IC deposits. Renal vessel wall deposits occurred at a dose of 0.313-5 mg thimerosal/L (18-295 microg Hg/kg bw/day), while splenic vessel wall deposits developed also in mice given the lowest dose of thimerosal, 0.156 mg/L (9 microg Hg/kg bw/day). The latter dose is 3- and 15-fold lower than the dose of Hg required to induce vessel wall IC deposits in genetically susceptible H-2s mice by HgCl2 and thimerosal, respectively. Further studies on the exact conditions needed for induction of systemic IC deposits by low-dose organic mercurials in autoimmune-prone individuals, as well as the potential effect of these deposits on the vessel walls, are warranted."

Hopefully, by citing these additional papers *published in journals readily available to you*, we hope that you will now see that the issue the **CoMeD** petition is addressing is the issue of Thimerosal toxicity in animal models at low levels of exposure that directly bear of the issue of Thimerosal safety in vaccines and other drugs.

"Moreover, if the vaccine is indicated for a population that includes females of childbearing potential, vaccine manufacturers are encouraged to perform additional special nonclinical studies in animals to evaluate the potential of the vaccine to harm the developing fetus."

The **CoMeD** reviewers find your statement here problematic because it indicates that, for vaccines, you are failing to properly discharge your duty, under **42 U.S.C. Sec. 262(a)(2)(C)**,[53] to ensure that vaccines are safe for the fetus when you authorize any vaccine, except for rabies, to be administered to a healthy pregnant woman who is disease free and has little, or no, risk of contracting a disease that threatens the life of the fetus.

Since, *based on your statement*, "*vaccine manufacturers are encouraged to perform additional special nonclinical studies in animals to evaluate the potential of the vaccine to harm the developing fetus*," you are admitting that you are *knowingly* failing to require some proof a vaccine is safe for the fetus when you authorize a vaccine to be used in pregnant women without such proof.

Hopefully, the pregnant American women and American women of childbearing age and their husbands, parents, and other relatives, will, *upon understanding your knowing failure to require vaccines you authorize to be given to pregnant women to be safe for their fetus*, be appropriately angered by your lack of concern for the safety of their unborn children.

Also, the **CoMeD** reviewers find it odd that, despite your claim that animal models should be used "*to evaluate the potential of the vaccine to harm the developing fetus*," in the case of the Rho(D) drug products that contained Thimerosal in

---

Let-6 See www.fad/gov/oc/initiatives/criticalpath, Critical Path Initiative, 69 Federal Register 21839, April 22, 2004).

53 **42 U.S.C. Sec. 262(a)(2)(C)** states (with underlining added for emphasis, "The Secretary shall approve a biologics license application -
(i) on the basis of a demonstration that -
(I) the biological product that is the subject of the application is safe, pure, and potent; …"

doi: 10.1588/medver.2007.04.00145

the past and, *presently*, in the case of the Thimerosal-containing influenza vaccines (now, 3 that are Thimerosal-preserved and 3 that have reduced levels of Thimerosal), you have approved all these Rho(D) biological products and inactivated-influenza vaccines, *supposedly, required to be the "safest medicines" because they are given to healthy persons to prevent contracting influenza in the future*, for routine administration in pregnancy without requiring these be evaluated for fetal safety in animals and/or humans as their "Pregnancy Class C" designation clearly establishes.

"However, currently available animal models are limited in terms of their ability to detect rare toxicities, or specific toxicities that may occur in a human subpopulation. To improve on this situation, FDA is working with manufacturers to develop better animal models and assays to measure activity and potential drug-induced toxicity at an early stage in product development."[Let-6]

Based on your statements here, the **CoMeD** reviewers hope that you will require the manufacturers of Thimerosal-preserved biologicals as well as the makers of any drug product that uses Thimerosal in the process used to produce the drug product to comply with **21 CFR § 610.15(a)** and prove that the finished drug formulation is "*sufficiently nontoxic*" by using SJL/J mice as the animal model because this animal model has clearly been proven its "*ability to detect rare toxicities, or specific toxicities that may occur in a human subpopulation*" when it comes to mercury poisoning by Thimerosal or other mercury-based compounds.

"Although FDA supports the goal of developing predictive models for nonclinical safety assessments, currently available state-of-the-art test systems would not be able to provide proof of the safety and efficacy of a product formulation as you requested (page P-2 of your petition)."

Since the "SJL/J mouse" animal model exists and is appropriately predictive of Thimerosal toxicity in susceptible humans in that it produces symptoms, behaviors, and brain morphology changes for low-dose Thimerosal exposure that match those seen in mercury poisoning, we must respectfully disagree with the your unsupported assertion here concerning the lack of a suitable model.

"FDA acknowledges that it would be useful if nonclinical models were developed that could be used to predict the safety of a biological or drug product in human subjects. However, to date there are no adequate and relevant models that would predict the risk that a vaccine will cause neurological damage, such as autism, in humans."

Obviously, here, you are attempting to:

- Ignore the elephant that Hornig's SJL/J mouse model represents and
- Change the petitioner's request from proof that the compound used as a mercury-based preservative, Thimerosal, is safe at the preservative level (or a lower level) into a general "*risk that a vaccine will cause neurological damage…, in humans*,"

because the "SJL/J mouse" model did prove that there is a mercury-poisoning risk for Thimerosal-preserved vaccines dosed according to the 2001 US national childhood vaccination schedule.

Moreover, since, *by definition*, autism is a "causeless" disorder, we find that you have either: **a)** *inappropriately* asserted that autism is caused by neurological damage or **b)** are now claiming that the "cause" of autism is "*neurological damage*" such as that caused by Thimerosal-derived mercury poisoning.

"As discussed above, you have suggested using the SJL/J mouse model for such evaluations (page P-5 of your petition). The SJL/J mouse is genetically predisposed to auto-immune diseases, which you hypothesize are an underlying cause of autism."

We find that you are being knowingly duplicitous in your remarks here because *neither* Hornig *et al*. *nor* the **CoMeD** petitioners have ever hypothesized that autoimmune diseases are an underlying cause of autism – only you have made such statements as the record clearly shows.

Factually, Hornig *et al*. and the **CoMeD** petitioners have stated that scientific evidence supports the reality that the developing brain, *in susceptible individuals*, is "uniquely susceptible to the neurotoxic hazard posed by" Thimerosal at preservative levels in vaccine formulations.

Factually, Hornig *et al*. only hypothesized, *as they clearly state in the abstract of their article*:

" We hypothesized that autoimmune propensity influences outcomes in mice following thimerosal challenges that mimic routine childhood immunizations."

Therefore, the **CoMeD** reviewers find that your "*hypothesis*" statement is clearly at odds with the facts and the statements made by the **CoMeD** petitioners.

doi: 10.1588/medver.2007.04.00145

At best, your apparent knowing distortion of the facts indicates that you have again failed to "carefully read" the **CoMeD** petition.

"However, to the best of our knowledge, there are currently no data providing evidence of auto-immune mediated central nervous system (CNS) damage in the brain of autistic patients."

While we do *not* disagree with your knowledge here, we note that your statement has nothing to do with the claims asserted by Hornig *et al*. or the **CoMeD** petitioners.

At best this statement should be ignored by the reader because it does *not* address the issues actually raised by the **CoMeD** petitioners but rather speaks to a hypothesis that you, and *not* Hornig *et al*. or the **CoMeD** petitioners, have raised.

"Therefore, even though these rodent models have value in understanding some of the processes by which exogenous agents may potentially exert adverse effects, we have no basis to extrapolate these findings to neurodevelopmental disorders in humans."

The **CoMeD** reviewers find your conclusion is based on a foreign hypothesis that you have fashioned from "whole cloth" and is, therefore, non-responsive to the issue raised by the **CoMeD** petitioners.

Factually, *as* **CoMeD** *has plainly asserted*, the "SJL/J mouse" model has clearly been established to be a valid animal model for assessing the "neurotoxic hazard posed by" Thimerosal at preservative levels and lower in vaccine formulations to the developing brain in susceptible individuals.

Since: **a)** as you admit and we agree, "*these rodent models have value in understanding some of the processes by which exogenous agents may potentially exert adverse effects*" and **b)** the outcomes observed (symptoms, behaviors, and brain abnormalities) parallel those seen in developing humans and other animals who have been mercury poisoned by Thimerosal or other mercury-based compounds, you do have a valid basis to extrapolate these mercury poisoning findings to Thimerosal-induced mercury poisoning in humans.

Since the preceding extrapolation applies to Thimerosal-induced mercury poisoning in developing animals from Thimerosal at preservative and lower levels for susceptible individuals, SJL/J mice in this case, it is obvious that, *for Thimerosal and mercury-based compounds*, this animal model can be used to:

- Establish the "sufficiently nontoxic" level of Thimerosal exposure for susceptible fetuses, neonates, babies, toddlers, preschoolers, children of school age, and adolescents required to satisfy the clear requirements of **21 CFR 610.15(a)**,
- Meet the government's statutory mandate to reduce the risk of adverse reactions in childhood vaccines set forth in **42 U.S.C. Sec. 300aa-27(a)(2)**, and
- Prove the toxicity of Thimerosal to susceptible individuals to ensure that only a "safe" level of Thimerosal or other mercury-based compound (*e.g.*, PMA or Calomel) is present in any drug's formulation.

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

Since:

- The fundamental paradigm, which **CoMeD** representatives have *repeatedly* asserted to the federal government and others, is:
  "Giving Thimerosal (49.55% mercury by weight)-containing drugs to humans mercury-poisons all of the recipients to some degree and some "susceptible" recipients to the point that they exhibit one or more of the clinical symptoms of mercury poisoning including, *in some instances*, the set of mercury-poisoning symptoms that are used to diagnose autism," and
- **CoMeD** petitioners have cited these references as evidence that supports or, *as required by **21 CFR § 10.30***, purports to refute, the issues CoMeD raised,

the **CoMeD** reviewers see no valid reason for you to state:

"*The references cited that report an increase in the autism rate do not link any increase to vaccines, ...*"

doi: 10.1588/medver.2007.04.00145

Moreover, we find that the "*references cited that report an increase in the autism rate*" do, ***in fact***, support petitioners' argument (paradigm), which in simplistic terms boils down to "administering mercury compounds, *like Thimerosal and PMA (or, in the previous American mercury-poisoning epidemic, Calomel)*, to humans mercury-poisons all of them to some degree and some to the degree that they exhibit one or more of the clinical symptoms of mercury poisoning."

Finally, we note that the isolated sections of the **CoMeD** petition that you are addressing here are sections presented in the overall context stated in the heading on P-7 of the **CoMeD** petition, "**A. Safety Not Proven**," for Thimerosal, or other mercury-based compounds, in vaccines and other drugs, but we find that your remarks address the sections you cite here without addressing them in the context within which they were presented, – "**Safety Not Proven**" under the rubric set forth in **21 CFR 610.15(a)**, '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.'"

Thus, the **CoMeD** reviewers have addressed your comments from the point of view of that referential context.

"On pages P-37 to P-39 of your petition, under your headings "The Link Between Thimerosal And Neurological Disorders" and "Autism Alarm", you quote reports from California's Department of Developmental Services, and the Department of Health and Human Services, CDC, and the American Academy of Pediatrics to demonstrate that the incidence of autistic spectrum disorders (ASD) in the United States has increased (endnotes 54, 55, and 56). FDA acknowledges these data; however, the observed increase in autism rates is difficult to interpret."

Since the **CoMeD** petitioners were using these autism, and other neurodevelopmental, rates as markers for the underlying mercury-poisoning caused by Thimerosal in vaccines, the **CoMeD** reviewers understand that, *while properly interpreting them was not without challenge*, these rates were *not* difficult to interpret.

"We note that the report of the California Department of Developmental Services stresses that the information in the report 'should not be used to draw scientifically valid conclusions about the incidence or prevalence of ASD in California' and that 'the number of persons with ASD described … do not constitute formal epidemiological measures of incidence or prevalence.'"

We note that that, *factually*, the section headed, "***The Link Between Thimerosal And Neurological Disorders***":

- Simply addressed the California DDS' April 2003 report, which "supported the interpretation that the increased prevalence of autism in California:" **a)** "is a valid phenomenon" and **b)** "is derived by factors beyond improved identification and diagnosis," and
- Reported that, "in February 2004, the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (CA OEHHA) **reaffirmed**" **petition endnote 55** "that, *under California Proposition 65*, **mercury and mercury compounds**, *including ionic mercury salts, ethyl mercury and Thimerosal*, had been and **are** properly classified as **reproductive toxins**."

Similarly, the **CoMeD** reviewers found that the section headed, "***Autism Alarm***," simply reported the factual information in the Autism A.L.A.R.M. jointly issued by several federal governmental agencies and the American Academy of Pediatrics, and noted:

"Based on the autism sex ratio reported by Verstraeten" **petition endnote 33** ", ***more than*** 80 % of the diagnosed autistic children are male."

Thus, we are at a loss to see the relevance of your statements:

"*We note that the report of the California Department of Developmental Services stresses that the information in the report 'should not be used to draw scientifically valid conclusions about the incidence or prevalence of ASD in California' and that 'the number of persons with ASD described … do not constitute formal epidemiological measures of incidence or prevalence.'*"

to the information provided by the **CoMeD** petitioners in these sections.

"Furthermore. the reports did not address the causes of this increased prevalence and the issues and factors related to the etiology of autism."

Since the **CoMeD** petitioners made no such claims here, we are at a loss to see your justification for making this non-relevant comment.

doi: 10.1588/medver.2007.04.00145

"Notably, none of these reports establishes a causal link between thimerosal and neurological disorders as suggested by you."

Since the **CoMeD** petitioners made no assertions of "*a causal link between thimerosal and neurological disorders*" in this section, the **CoMeD** reviewers are again at a loss to see the relevance of your statement in what, *you claim*, is a discussion of pages "*P-37 to P-39*" of the **CoMeD** petition.

"Moreover, as discussed above in section I.C.2, if it is true that autism rates are increasing, such a fact would contradict, rather than support, your contention that thimerosal in vaccines cause autism, given that the amount of thimerosal that children receive through vaccines has decreased dramatically."

First, we note that:

- This petition makes no contention that "(*T)himerosal in vaccines cause* [sic; causes] *autism*" in the sections of the **CoMeD** petition you are citing, and
- The "*contention*" that you find problematic was enunciated by Congress in a report,[7] titled "MERCURY IN MEDICINE—TAKING UNNECESSARY RISKS," which was entered into the *Congressional Record* by the "Subcommittee on Human Rights and Wellness, Committee on Government Reform of the House of Representatives" in May 2003.

Second, the **CoMeD** reviewers note that your, "*given that the amount of thimerosal that children receive through vaccines has decreased dramatically*," is *not* supported by any actual nation-wide U.S. vaccination-experience data of which we are aware or which you have provided, published, or cited.

Factually, The Thimerosal-preserved vaccines were *not* recalled and destroyed when the "reduced Thimerosal," "trace Thimerosal," and "no Thimerosal" vaccines were slowly introduced as replacements for the corresponding "Thimerosal-preserved" vaccines.

At best, the maximum amount of Thimerosal that children received only started to decline after 2000.

In addition, by:

- Conditionally ("when feasible"[14]) adding the Thimerosal-preserved inactivated-influenza vaccines to the U.S. recommended childhood immunization schedule, in 2002, for children 6-months to 23-months of age and pregnant women in their second and third trimesters during the "flu season,"
- Fully adding these Thimerosal-preserved "flu" vaccines to the U.S. recommended childhood immunization schedule in December 2003 for children 6-months to 23-months of age and pregnant women in their second and third trimesters during the influenza season, and,
- In 2006, increasing the age range for children to 6-months to 59 months of age and including all pregnant women who are pregnant during the "flu season" without regard to their stage in pregnancy,

you have *significantly* offset the drop and rate of drop in the maximum level of Thimerosal exposure such that the effective maximum Thimerosal exposure has definitely *not* "*decreased dramatically*."

Based on the **CoMeD** reviewers' discussion of the specific dose (dose divided by the subject's body weight) and its approximate impact on toxicity (**see** pages S-R-18 and S-R-19 of this review document), we find the reality may be your actions have actually, *in effect*, increased the maximum toxicity that children may experience because you have knowingly approved, *in deliberate disregard for the absolute need for proof of safety to the fetus*,[54] the administration of Thimerosal-preserved inactivated-influenza vaccines to pregnant women.

Finally, we find that you have taken these actions even though you *knew* (*as that term is defined in **21 U.S.C. Sec. 321(bb)***) that the inactivated-influenza vaccines are *not* effective.

Moreover, as discussed on pages S-R-34 and S-R-35 of this review, the valid data points[37] in the article by Fombonne et al.[36] did support the reality that the incidence for PDDs declined significantly after the Canadian government replaced several Thimerosal-preserved vaccines with a multivalent "Thimerosal free" vaccine.

---

[54] Since Thimerosal is a proven human teratogen, mutagen and carcinogen at Thimerosal levels at or below 1 ppm, it should be obvious that for this highly toxic material, appropriate toxicological safety testing is an absolute must for Thimerosal-preserved vaccines administered to pregnant women.

doi: 10.1588/medver.2007.04.00145

Finally, in epidemiological studies conducted by Geier and Geier[55,56,57] using CDC-recognized methodologies, these peer-reviewed published papers found that the incidence rates of various neurodevelopmental conditions did begin to decline in the 2001 – 2004 timeframe, after the maximum level of Thimerosal exposure (in terms of children inoculated and Thimerosal-preserved vaccines administered) was reached in the 1999 to 2000 timeframe and then began to decline.

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

First, we again note that, contrary to your repeated attempts to paint the **CoMeD** petitioners as arguing, *as you state*, "*thimerosal in vaccines cause* [*sic*; causes] *autism*," **CoMeD** petitioners have simply stated that the evidence is clear to them that:

> "Giving Thimerosal (49.55% mercury by weight)-containing drugs to humans mercury-poisons all of the recipients to some degree and some "susceptible" recipients to the point that they exhibit one or more of the clinical symptoms of mercury poisoning including, *in some instances*, the set of mercury-poisoning symptoms that are used to diagnose autism,"

or, simplistically, Thimerosal (49.55% mercury by weight) mercury poisons those administered drugs containing Thimerosal.

In addition, we note that the isolated section of the **CoMeD** petition that you are addressing here is a section presented within the overall context stated in the heading on P-7 of the **CoMeD** petition, "**A. Safety Not Proven**," for Thimerosal, or other mercury-based compounds, in vaccines and other drugs, but we find that your remarks address the section you cite here without addressing said section in the context in which they were presented – "**Safety Not Proven**" under the rubric set forth in **21 CFR 610.15(a)**, '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,'".

Thus, the **CoMeD** reviewers have addressed your comments in that referential context from **CoMeD**'s viewpoint concerning the nature of the problem being addressed.

"On pages P-39 to P-42 of your petition under your section 'Clinical Evidence', you have stated that 'growing clinical evidence strongly suggests that many, it not most, of these damaged children are members of a genetically vulnerable, mercury-sensitive subpopulation that have been, and are being injured by: a. The mercury-based preservatives in vaccines with which they have been immunized and/or, b. In utero, by the mercury-based preservatives in some of the drugs prescribed to and/or used by their mothers.' You cite studies by *Bradstreet, et al. (2003)*, and *Holmes, et al. (2003)* (your endnotes 57 and 41), to support your position."

We find that, *in the context of the lack of proof of the safety of Thimerosal in vaccines*, your statements accurately reflect the assertion made by **CoMeD** and the references cited to support it.

"*Holmes, et al.* postulated that an impaired mercury excretion might be an important susceptibility factor underlying recent increases in autism. They evaluated mercury concentrations in first baby hair cut samples from 94 autistic children and 45 age- and gender-matched controls. Control samples were collected under the condition that the child received all their childhood vaccinations on schedule, so that they would show comparable postnatal exposure levels. **Notably, this study did not attempt to examine the role of childhood vaccine exposure in autism."**

Factually, *as the researchers stated in their abstract* (with underlining added to highlight the key points addressed):

> "Reported rates of autism have increased sharply in the United States and the United Kingdom. One possible factor underlying these increases is increased exposure to mercury through thimerosal-containing vaccines, but vaccine exposures need to be evaluated in the context of cumulative exposures during gestation and early infancy. Differential rates of postnatal mercury elimination may explain why similar gestational and infant exposures produce variable neurological effects,"

---

55 Geier DA, Geier MR. Early downward trends in neurodevelopmental disorders following removal of Thimerosal-containing vaccines. ***J Am Phys Surg***. 2006 Spring; **11**(1): 8-12.

56 Geier DA, Geier MR. An assessment of downward trends in neurodevelopmental disorders in the United States following removal of thimerosal from childhood vaccines. ***Med Sci Monit***. 2006 May 29; **12**(6): CR231-CR239 [Epub ahead of print].

57 Geier DA, Geier MR. A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. ***Neuro Endocrinol Lett***. 2006 Aug 30; **27**(4), in press. [Epub ahead of print].

doi: 10.1588/medver.2007.04.00145

Thus, based on the outcome of their study, Holmes *et al*. actually "*postulated*" that differences in mercury elimination explained why similar gestational and infant exposures to Thimerosal-derived "mercury" ("through thimerosal-containing vaccines") "produce variable neurological effects."

Thus, this research addressed "variable neurological effects" (and *not*, *based on your continued insertion of a diagnostic label used for a supposedly "causeless" psychiatric disorder*, autism *per se*) related to mercury excretion, *or more precisely*, impaired excretion.

Thus, they simply used the psychiatric label "autism" to identify a group of children with similar fairly severe "neurological effects" profiles.

With respect to your:

"***Notably, this study did not attempt to examine the role of childhood vaccine exposure in autism***,"

the **CoMeD** reviewers note that the researchers reported:

"Information on diet, dental amalgam fillings, vaccine history, Rho D immunoglobulin administration, and autism symptom severity was collected through a maternal survey questionnaire and clinical observation."

Thus, we find that the researchers simply used a diagnosis of "autism" to find their group of test subjects and a complete vaccination history to find their matched controls so that they might study these groups to elucidate, *for similar vaccine-mercury exposures in both the test and the control groups*, the differences, if any, in the elimination factors and patterns that differentiate the two groups.

Since they recorded information on "diet, dental amalgam fillings, vaccine history, Rho D immunoglobulin administration, and autism symptom severity" and matched the controls based on their vaccine-mercury exposure history, it is clear that these researchers were principally interested in determining the role of mercury excretion on the severity of the neurological effects.

Since the difference in population susceptibility is one of the key issues that **CoMeD** raised, this study was included because it goes to the heart of that contention.

Therefore, we fail to see the import of your remark here because it is obviously *not* relevant to the issue this study addressed.

"First baby hair cut samples had been collected by the parents with a mean age at haircut of 17.7 months. Hair mercury levels in autistic children were significantly lower than in controls (0.47 ppm versus 3.63 ppm). Subgroup analysis showed decreased mercury levels in the hair as the autism severity score increased. The lower level of mercury content in baby hair was not caused by less exposure, as the autistic infants were exposed to higher levels of mercury during gestation, through dental amalgams or RhoD immunoglobulin injections in the mother."

Here, we are in agreement.

However, as the researchers found, it is *not* the level of mercury exposure but the differences in the level and pattern of mercury excretion that differentiates the test group from the matched control group.

Moreover, since, *as you report*, "*(s)ubgroup analysis showed decreased mercury levels in the hair as the autism severity score increased*," this research supported the reality that among the children with significant neurological impairment the severity of the neurological impairment was, *on average*, inversely proportional to the level of mercury found in the children's hair samples.

Further, we note you failed to report or address the findings:

- "Hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish consumption as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group,"
- "Within the autistic group, hair mercury levels varied significantly across mildly, moderately, and severely autistic children, with mean group levels of 0.79, 0.46, and 0.21 ppm, respectively," and
- "Hair excretion patterns among autistic infants were significantly reduced relative to control."

Based on these findings, it seems clear to the **CoMeD** reviewers that this study has established the existence of both variable susceptible to mercury-poisoning related neurological impairment among humans and, for those, who

doi: 10.1588/medver.2007.04.00145

exhibited obvious adverse clinical "neurological effects" – those in the test group – a rough inverse correlation between the level of mercury in their hair and the severity of their mercury-poisoning-related neurological impairment.

"As stated by the authors, there are certain limitations to the study, i.e., the study was not of prospective design, recruitment of autistic study subjects was influenced by medical care-seeking behavior, testing facilities were not under the direct control of the investigators, and the population studied may not be representative of the autism population of the whole. Furthermore, it is noted that the "first baby hair cut" hair sample was obtained at a mean age of 17 months and thus, the implications of mercury measurements for prenatal exposures is unclear (see also 2004 IOM report). In addition, infant exposures to other sources of mercury postnatally were not ascertained."

While these are issues that the researchers raised, they do not detract from their finding that there significant "mercury elimination" differences between those children that do *not* have evidence of adverse clinical "neurological effects" (the control group children) and those who were exhibiting adverse clinical "neurological effects" with respect their excretion of mercury in their hair, including the large contribution from Thimerosal-preserved vaccines that these children would have received since they all were fully vaccinated and born between 1985 and 1999 when all Thimerosal-containing vaccines were Thimerosal-preserved vaccines. [**Note:** Though the clinical-neurological-symptom-free controls, born between 1990 and 1999, were also fully vaccinated according to the prevailing national schedule, they were found to be mercury excreters. In general, the level of mercury excreted in their hair tracked the number of amalgam fillings their mothers had during pregnancy (probably "inorganic mercury" they had accumulated from their mothers during gestation) with an offset that was probably related to the excretable circulating "inorganic" mercury from the Thimerosal-mercury ("organic mercury") they received during vaccination with Thimerosal-preserved vaccines.]

"The authors' hypothesis — that children with autism do not 'excrete' mercury into the hair and that therefore, mercury burden remains bioactive within the body — was not supported by data."

First, the **CoMeD** reviewers note that you have fabricated the hypothesis you state here because it is *not* the working hypothesis that the researchers, *at the end of their introductory remarks*, clearly state was used (with underlining added for emphasis):

"… we believe that our study design effectively examines the null hypothesis of no differential excretion rates in the hair of infants subsequently diagnosed with autism."

Their findings clearly rejected this "null hypothesis" and established the validity of the alternative hypothesis – "there exist differential excretion rates in the hair of infants subsequently diagnosed with autism as compared to 'normal' controls."

In addition, whether or not mercury is excreted into the subject's hair at some level, the mercury remaining in each subject's body, control and test, remains bioactive.

Since the article does *not* contain the phrase, "*mercury burden*," or even contain the words "*bioactive*," "active," or "activity" and, *as far as we can ascertain these topics were neither germane to this study or addressed by it*, we find that the hypothesis you state here is an obvious "whole cloth" fabrication on your part – a fabrication that: **a)** has no validity and **b)** is at odds with the actual hypothesis tested as well as the valid and instructive findings of this study.

"Neither the authors nor any other studies, to our knowledge, have established that children who have relatively small amounts of mercury in their hair are unable to excrete mercury, and retain unsafe amounts of mercury in their bodies."

While your non-relevant assertion here may technically be true, we note that so is the following assertion:

"Neither the authors nor any other studies, to your knowledge, have established that children who have relatively large amounts of mercury in their hair are unable to excrete mercury, and do *not* retain unsafe amounts of mercury in their bodies."

since, *based on the findings of this study*, there is no proof that there is any correlation between: **a)** the level of mercury in a hair sample and **b)** the level of mercury burden in the person who provided the hair sample.

Thus, we find:

- Your statement here fails to address any issue relevant to the findings of this study,
- The study's findings have definitively establish that: **a)** there is a susceptible segment of the population, who, *relative to the majority of the population*, have an impaired ability to excrete mercury in their hair; and **b)** *to a first approximation*, the level of mercury in the hair samples of those who have impaired excretion is inversely proportional to the severity of the neurological impairment that they exhibit, and

doi: 10.1588/medver.2007.04.00145

- There is no *a priori* correlation between the level of mercury in person's hair and the level of mercury in their body, in general, or in the brain, heart, kidney, lung, pancreas, thymus, pituitary gland, or other organ, in specific.

Therefore, this study has clearly established that:

- There is an individual (genetic) variability component that, *for a given general level of low-level Thimerosal-mercury exposure*, separates those who have neurological injuries from those who do not, and
- Within those who have clinical levels of neurological injury, there is a general inverse relationship between the level of mercury excreted in their hair and the severity of their clinical neurological injury.

Finally, *as the* **CoMeD** *petitioners noted*, "Based on the hair results, it seems obvious that the mercury detoxification and" [hair] "excretion patterns among autistic" [neurologically injured] "infants were significantly reduced relative to those of the matched control infants."

"*Bradstreet, et al.* evaluated the concentration of mercury in the urine following a 3 day treatment with an oral chelating agent in children with autistic spectrum disorders in comparison to a control population. Urinary mercury concentrations were significantly higher in 221 children with autistic spectrum disorder than in 18 normal controls. Furthermore, in a sub-analysis, where cases were matched to vaccine status, vaccinated children with ASD had higher urinary mercury concentrations than the group of matched vaccinated controls."

In general, the **CoMeD** reviewers find that you have properly presented the findings for the results from the oral chelation of fully vaccinated children diagnosed with an ASD (autism spectrum disorder) with DMSA as compared to a mixed set of controls, some fully vaccinated with no evidence of a clinical neurological impairment and the others were children who had never been vaccinated.

All that the study found was that, *on average*, after a short-term chelation challenge, the urine of the chelated ASD children contained statistically more mercury than the control children, while, *for cadmium and lead*, the excreted levels were, *on average*, statistically the "same"

As before, we find that the **CoMeD** petitioners offered this paper as further proof of their assertion that, *in general*, the retention and excretion of mercury for children diagnosed with an ASD is different than the retention and excretion of mercury for children who are "normal" with respect to exhibiting the clinical symptoms used to diagnose an ASD, whether fully vaccinated or not vaccinated at all.

Based on these findings, we find that this study has confirmed the **CoMeD** petitioner's assertion that those children who have neurological damage that exhibits as the symptoms used to diagnose an ASD retain mercury more than "normal" (control) children who show no evidence of any clinical level of neurological damage.

"As pointed out by the IOM (see 2004 IOM report), the range of mercury excreted was 0-59 with a mean of 4.1 μg mercury/g creatinine and a standard deviation of 8.6, suggesting that data might he skewed in the direction that most of the children with autism excrete little mercury."

First we find that, *absent any segregation of the children with autism from the ASD group*, there is no valid basis for your (or the 2004 IOM report's) assumption "*that most of the children with autism excrete little mercury*" because this article presents no separate data for those diagnosed with autism.

"*Bradstreet, et al.* speculate that their results and those of Holmes (see above) might result from a decreased ability of children with autistic spectrum disorders to excrete mercury. The authors conclude that mercury levels measured could 'plausibly have resulted from exposure to mercury in routine childhood vaccines in the United States and thimerosal in RhoD immune globulin and other potential environmental sources of mercury may be contributory.' According to the hypothesis of the authors (Bradstreet, et al., and Holmes, et al.) thimerosal provides a source of mercury, which a subpopulation of autistic children are unable to process, thus leading to higher mercury burden."

In general, the **CoMeD** reviewers find that you have properly reflected these researchers views about the possible link between the level of Thimerosal exposure from vaccines and the clinical symptoms of neurological injury that are: **a)** the same or similar to the symptoms seen in sub-acute mercury poisoning cases and **b)** used to diagnose an ASD.

"It is noteworthy that these papers do not provide any causal link between the thimerosal contained in vaccines and autism; exposure to thimerosal as a result of vaccination was not directly addressed or studied."

Since the issue the **CoMeD** petitioners were using these papers to address was the variation in the ability of children to metabolize and excrete Thimerosal and other mercury-based compounds (such that those with diagnosed clinical

doi: 10.1588/medver.2007.04.00145

neurological injury are typically found to have "impaired" ability to detoxify themselves from a bolus dose of a mercury-containing compound and excrete the metabolism end product, "inorganic mercury," as efficiently as those who have never been vaccinated or, if vaccinated, exhibit none of the clinical symptoms used to diagnose an ASD or other behavioral difficulty), the fact that these papers "*do not provide any causal link between the thimerosal contained in vaccines and autism*" or "*exposure to thimerosal as a result of vaccination was not directly addressed or studied*" are *not* germane to this issue.

Therefore, because these remarks do *not* address the issues raised by **CoMeD** here, we find that these non-relevant remarks should simply be ignored.

"Given that thimerosal is no longer present in childhood vaccines, other than in trace amounts in a few vaccines and in limited amounts in seasonal influenza vaccines, FDA concludes that even if their unproven hypothesis about autistic children's mercury excretion ability is correct, the contribution of vaccine-related mercury to total mercury burden and toxicity is not significant."

First, we find that your self-serving remarks ignore the reality of the hundreds of thousands of children who were injected with several courses of Thimerosal-preserved vaccines and have been mercury-poisoned by their inoculations to the point that they exhibit the recognized symptoms of mercury poisoning that are essentially the same as the symptoms that are used to diagnose autism[58] or other neurodevelopmental disorders and behavioral problems that the healthcare establishment claims are "causeless," *in spite of this obvious and proven linkage* (*i.e.*, the reality that inoculating babies with mercury-based compounds mercury poisons all to some degree because no safe level has been established for mercury exposure in any baby much less in "susceptible individuals").

Thus, we find that your rhetoric here is attempting to simply write off all those harmed by Thimerosal-preserved biological products that were licensed and approved without being required to meet the clear CGMP requirement minimum set forth in **21 CFR § 610.15(a)** that the "shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient."

Second, we find that, as we have already established (**see** pages S-R-15 through S-R-19 in this review), contrary to your "*Given*" assertion, "*thimerosal is no longer present in childhood vaccines, other than in trace amounts in a few vaccines and in limited amounts in seasonal influenza vaccines*," because of the current national childhood vaccination's recommendations, the maximum level of Thimerosal today's child receives by age 5 is more than 50% of the 187.5-µg dose that a typical child born to a mother who received no Rho(D) inoculation in 1995-1996.

Moreover, *when that child's mother is vaccinated with a Thimerosal-preserved influenza vaccine while she was pregnant with that child*, the 50-µg dose of Thimerosal that pregnant woman receives is (*depending on the size [weight] and developmental stage of the fetus when she is inoculated*) as, or more, toxic to that developing child than the post-natal immunizations with the Thimerosal-preserved influenza vaccines administered, *according to the current recommended childhood vaccination schedule*, from the time the child is 6-months old until that child is 5 years of age.

Since recent studies have again confirmed that the inactivated-influenza vaccines are *not* effective in preventing children[24] or, *for that matter*, the general public[20] from getting or spreading influenza, we find that your continued approval of influenza vaccines to be marketed is at odds with not only the clear requirements for proof of safety but also for ongoing proof, based on population experience, that said vaccines are truly effective in preventing those inoculated from getting or spreading influenza – something that influenza vaccines have been shown *not* to be.[20]

In addition, we find your "*the contribution of vaccine-related mercury to total mercury burden and toxicity is not significant*" is an attempt to equate "*total mercury burden*"[59] to "*toxicity*" without addressing the critical difference between a long-term accumulation of mercury from sources having much lower levels of mercury and are mostly from elemental mercury and inorganic mercury ingested and bolus doses of drug formulations containing 10 to 100 times the readily available organic mercury level as those background sources(including protein bound methylmercury species found in the fish that humans ingest) injected into and rapidly soluble in the human body.

We find that this transparent attempt to distort toxicological reality is beneath contempt.

---

[58] The parallels between the symptoms of sub-acute mercury poisoning and the symptoms attributed to autism are clearly outlined in **Appendix A** of the article posted at: http://www.mercury-freedrugs.org/docs/Thimerosal_Causes_Mercury_Poisoning.pdf.

[59] Bingham M, Copes R. Thimerosal in vaccines Balancing the risks of adverse effects with the risk of vaccine-preventable disease. ***Drug Safety*** 2005; **28**(2): 89-101.

doi: 10.1588/medver.2007.04.00145

In simplistic terms, using your "*Tylenol*" as an example, you are attempting to equate the toxicity of a child's being intermittently given one recommended dose of Tylenol over the course of a day for short periods in the course of a year ("chronic exposure") to the toxicity from a child's being given 100 doses of that Tylenol all at once ("bolus dosing") at 10 to 100 times the year's chronic-exposure dose).

We note that the reality is, using your Tylenol example, such *bolus dosing* in a "susceptible" child could lead to death, or, *even in a "resistant" child*, liver failure, though the "daily" dosing regimen should be "safe" – causing no clinical level of liver damage – for both.

Similarly we find that bolus dosing, injecting 25- or 50- µg doses of Thimerosal when a typical Thimerosal-preserved vaccine is administered much more significantly mercury poisons a child than the typical less than 0.2 µg dose of inorganic mercury they may ingest during the course of a day from drinking potable water.

Hopefully, any reader, *as we have*, will see through and reject your attempt to mislead here as well as question your attempting to defend the unnecessary addition (*because there are other compounds [e.g., 2-phenoxyethanol], which are not the bioaccumulative teratogen that Thimerosal is, that vaccine makers can and do use as preservatives*) of a highly toxic substance, Thimerosal, to a vaccine formulation at levels more than 5,000 times higher than the "least-toxic level" for Thimerosal established when **CoMeD** petitioners filed this citizen petition[60] (**CoMeD** petition's endnote **6.A.3**) and more than 100,000 times higher than the current established "least-toxic level" for Thimerosal.[18]

"C. Arguments that Thimerosal in the Current Amounts is Insufficient to Qualify 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

You have raised concerns about the adequacy of thimerosal as an effective preservative and have cited epidemiologic and laboratory investigations of two clusters of streptococcal abscess after DTP vaccinations in Georgia and Oklahoma (Stetler, et al., 1985) (your endnote 21). You cite from the paper that the manufacturer's preservative effectiveness tests showed that at 4°C, 4.5% of the challenged Streptococcus survived l4 days after inoculation into a multi-dose DTP vaccine vial and you quote the authors that at 'currently used concentrations, thimerosal is not an ideal preservative' and 'because thimerosal is an organic mercurial compound, higher concentrations might reduce vaccine potency or pose a health hazard to recipients' (page P-14 of your petition)."

We find that you have accurately stated: **a)** the preservative issue, "*Thimerosal in the Current Amounts is Insufficient to Qualify as a Preservative*," in your title, and **b)** the findings reported, "*the manufacturer's preservative effectiveness tests showed that at 4°C, 4.5% of the challenged Streptococcus survived l4 days after inoculation into a multi-dose DTP vaccine vial*," in your narrative.

According to the United States Pharmacopeia (USP), the current ("Official 8/1/06 – 4/30/07") USP standard for a preservative, set forth in General Chapter <51> Antimicrobial Effectiveness, for "*Category 1 Products*" (defined as preservatives for "*Injections, other parenterals including emulsions, otic products, sterile nasal products, and ophthalmic products made in aqueous bases or vehicles*"), requires that, after 14 days of incubation at "22.5 ± 2.5ºC, "not less than a 3.0 log reduction from the initial count" or, *in laymen's terms*, no more than 0.1% of the initial count for "*Streptococcus*," and you report the researchers found "*4.5% of the challenged Streptococcus survived l4 days after inoculation into a multi-dose DTP vaccine vial*," 45 times the limit allowed.

Because you have cited no studies or other evidence to overcome the clear evidence in this reference and the lower temperature of incubation should *not* have decreased the survivability of the "*challenged Streptococcus*" by more than a factor of 4, the researchers' findings seem to support the reality that, *as the **CoMeD** petitioners asserted*, 0.01% Thimerosal in a released DPT-vaccine vial failed to meet the USP criteria for a preservative and, therefore, *contrary to your unsupported assertion*, does *not* meet the "*United States Pharmacopeia Standard for a Preservative where it is being used as One*."

In addition, the cited article by Stetler *et al*. from the CDC also stated:

"*The thimerosal preservative present in DTP vaccine requires substantial time to kill organisms and cannot be relied upon to prevent transmission of bacteria under conditions of practice when a vial is used over a short*

[60] Waly M, Olteanu H, Banerjee R, Choi S-W, Mason JB, Parker BS, Sukumar S, Shim S, Sharma A, Benzecry JM, Power-Charnitsky V-A, Deth RC, **IMMEDIATE COMMUNICATION**, Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal. ***Molecular Psychiatry*** 2004 January 27: 1-13. [Confirmation of Thimerosal Effects at Parts per Billion]

doi: 10.1588/medver.2007.04.00145

period. Instead, the most important means of preventing abscesses secondary to DTP vaccination is to prevent contamination by careful attention to sterile technique."

Clearly, these statements by CDC personnel support the reality that Thimerosal is *not* an effective multiple-dose-vial preservative because such vials require the preservative to provide protection until the vial's contents are used up to prevent needle contamination from contaminating the vial.

"FDA notes that the authors also concluded 'that no other preservatives that are currently available are as safe and effective as thimerosal.'"

First, we note that:

- *Neither* these researchers *nor* you provided evidence to support the validity of this statement,
- The issue of "*as safe and effective as*" is *not* germane to the issue of meeting the USP's definition of an effective preservative – which is a prerequisite for a compound's being used as a preservative in a vaccine formulation,
- Nothing prevents all vaccines from being packaged in a single-does presentation that does *not* require the addition of a preservative,
- *Since all currently approved preservative systems are, by their very nature, toxic to human tissues to some degree and, thereby, at a minimum, cause adverse reactions at the injection site*, under **42 U.S.C. Sec. 300aa-27(a)**, you should have started banning their use in all childhood vaccines in December of 1987 after this statutory mandate became effective <u>because</u> banning preservatives definitely lowers adverse reactions.

Additionally, the following are a series of historical studies that, *though they are readily available*, **a)** you have apparently failed to consider and **b)** clearly establish that Thimerosal, *at a level of 0.01%, or lower, in a biological product formulation*, is ineffective as a preservative:

1. A 1943 ***JAMA*** publication that questioned Thimerosal as a "preservative," concluded, "(i)n a recent study of protein sulfhydryl groups Hellerman, Chinard and Deitz point out that organometallic compounds of the type R-Hg-X…form poorly dissociated protein mercaptides by combination of the organic mercurial with proteins and thiol groups. According to Fildes the formation of such mercaptides is the basis for the bacteriostatic action of mercury. Such sulfhydryl groups are present, however, not only in bacteria but in plasma and other proteins. Bacteriostatic action of such organomercuric compounds in the presence of serum is therefore largely prevented by competition of reactive groups on the serum proteins for the mercury. This presumably is the basis of the funding that the 'activity of a mercurial antiseptic in serum is reduced to 0.33-0.0007 percent of its activity in saline.' Ignoring these chemical facts can be responsible for very serious occurrences, such as the arrival in England of plasma 'preserved' with 1:10,000 Merthiolate containing viable micro-organisms…In our experience 1:10,000 Merthiolate has not been able to insure the sterility of stored liquid plasma. The contaminations reported in this paper in plasma-saline mixture containing 1:10,000 Merthiolate are sufficient to be an argument against its use. The material found to be contaminated when tested after its arrival in England is further evidence that 1:10,000 Merthiolate cannot be considered the ideal preservative…"[61]
2. Morton *et al*. (1948), under a grant from the Council on Pharmacy and Chemistry of the American Medical Association, published an article on the bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci. They reported, "…the label on a bottle of 'Solution Merthiolate, 1:1,000, Stainless' purchased as recently as June 1947 states that it is 'a stable, stainless, organic mercury compound of high germicidal value, particular in serum and other protein media.' It is not highly germicidal and especially does not possess high germicidal value in the presence of serum and other protein mediums. The loss of antibacterial activity of mercurials in the presence of serum proves their incompatibility with serum… The comparative in vitro studies on mercurochrome, metaphen and Merthiolate on embryonic tissue cells and bacterial cells by Salle and Lazarus cannot be ignored. These investigators found that metaphen, Merthiolate and mercurochrome were 12, 35 and 262 times respectively more toxic for embryonic tissue cells than for Staphylococcus aureus. Nye and Welch also found the same three mercurial compounds more toxic for leukocytes than for bacterial cells. Not only is there direct toxic action of the mercurial compounds on the cellular and humoral components of the animal body, but there is also the possibility of sensitization."[62]

---

[61] Anonymous. 1943. Mercurials as 'preservatives.' *J. Am. Med. Assoc.* 122:1253.

[62] Morton, H. E., North, L L., and Engley, F. B. 1948. The bacteriostatic and bactericidal actions of some mercurial compounds on Hemolytic streptococci: in vivo and in vitro studies. *J. Am. Med. Assoc.* 136:37-41.

doi: 10.1588/medver.2007.04.00145

3. Engley (1950) of the Biological Department, Chemical Corps, Camp Detrick published an evaluation of mercurial compounds as antiseptics. Engley judged mercurials to be inadequate as antiseptics, "(m)ercurial compounds have not enjoyed a peaceful career as antibacterial chemicals since their popularization as germicides over sixty years ago (Kock, 1891)…During the ensuing years, other workers, using various techniques, have also shown that the antibacterial activity of mercurials is only slowly bactericidal and mainly bacteriostatic. This bacteriostasis is even nullified by the presence of many types of sulfur-containing compounds, including sulfides (Geppert, 1889), (Hunt, 1937), thioglycollate (Marshall, Gunnison, and Luxen, 1941), body fluids such as plasma (Johnson and Meleney, 1942), and other organic matter (Greeen and Birkeland, 1944)."

Furthermore, and of even greater concern, was Engley's conclusion that mercurials, such as Thimerosal, "…are ineffective in vivo and may be more toxic for tissue cells than bacterial cells, as shown in mice (Nungester and Kempf, 1942) (Saber, 1942) (Spaulding and Bondi, 1947), tissue culture (Salle and Catlin, 1947), and embryonic eggs (Witlin, 1942) (Green and Birkeland, 1944), and with leucocytes (Welch and Hunter, 1940)."[63]

4. Subsequently, Engley (1956) presented a paper to the 42nd midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago, Illinois.[64] Engley overtly questioned the acceptance of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating, "(t)he use of mercurials as preservatives in vaccines and antisera is of considerable interest. These chemicals are added to protect against the introduction of organisms in multi-use containers in particular. We have always wondered about their efficacy in that both vaccines and antisera contain reactive groups to tie up these compounds. In a series of continuing experiments over the past several years we have begun to evaluate various preservatives in serum and vaccines under conditions of use. Employing stock vaccines and serum with and without preservatives and stored at varying lengths of time a contaminating dose of representative sporeformer (*Bacillus subtilis*) in the spore stage gram negative rod (*E. coli*) and gram positive coccus (*S. aureus*) were added. While the mercurial preservatives had good activity on initial addition, after storage of three, six or more months decreasingly less to negligible residual activity appeared to be left, indicating that the chemical was tied up by the protein of the biological or otherwise inactivated. A check on a series of over one thousand bottles of various biologicals from clinics obtained after use revealed that up to five percent contained micro-organisms. This would suggest that once these biologicals are in the hands of users a problem still exists. Regarding preservatives, one of the real problems existing in hospitals and clinics is the need for good preservatives in the routine eye dilators and nasal preparations of the decongestant type. Routine checks of these indicate a high percentage of contaminated solutions. In one instance we had direct evidence of upper respiratory cross-infection from the use of a common nasal dropper preparation in a clinic."

Engley then gave an evaluation of the relative toxicity of mercurials, such as Thimerosal, by stating, "(t)he toxicity of chemicals used as drugs on or in the body has been of considerable interest since man first began exposing himself to various chemicals many years ago. Unfortunately there have not been good techniques for toxicity determinations of certain types of chemicals which might be really indicative of toxicity for humans...Graph 15 compares mercurial compounds and shows how they fit in with other compounds in toxicity...Mercurochrome appears to be the least toxic ranging down through Merthiolate...One point should be made here. Bichloride of mercury has always been pointed out as an extremely toxic mercurial and the organic mercurials were supposed to be much less toxic but according to these data we find bichloride right in the middle of the organic mercurials in regard to cell toxicity."

Finally, it should be noted, with respect to the toxicity experiments undertaken by Engley, that he determined Thimerosal was significantly toxic to human tissue culture cells at a concentration of 10 parts-per-billion (ppb).

5. Hekkens *et al*. (1983) undertook an evaluation of the effectiveness of some preservatives in inactivated human vaccines by application of the test described in the United States Pharmacopoeia (USP) XIX. These researchers described that five recommended strains as well as three strains isolated from vaccines were used as test strains. It was observed that vaccines preserved with Thimerosal did *not* fully meet the requirements for a vaccine preservative according to the criteria established by the USP XIX.[34]

6. Lowe and Southern (1994) evaluated the antimicrobial action of various preservatives for vaccines. They described, "(t)he preservative most commonly used is Thiomersal. Other preservatives are being evaluated because: (i) this material has become difficult to obtain; (ii) the use of mercury-containing compounds in

---

63 Engley, F .B. 1950. Evaluation of mercurial compounds as antiseptics. *Ann. N. Y. Acad. Sci.* 53:197-206.

64 Engley, F. B. 1956. *Mercurials as Disinfectants: Evaluation of Mercurial Antimicrobic Action and Comparative Toxicity for Skin Tissue Cells*. Chicago, IL: 42nd Mid-Year Meeting of the Chemical Specialties Manufacturer's Association.

doi: 10.1588/medver.2007.04.00145

> medicinal products is considered potentially harmful; and (iii) it has been found that some vaccine components are unstable in the presence of this material."
>
> In light of these facts, the researchers undertook a series of experiments comparing the antimicrobial activity of phenoxyethanol with Thimerosal in diphtheria, tetanus, and pertussis (adsorbed) vaccine. It was observed, "(b)oth chemicals were equally effective in inactivating challenge doses of Gram-negative and Gram-positive micro-organisms, as well as yeast." Furthermore, it was reported, "the low toxicity of phenoxyethanol in children has been reported…"[35]

"FDA wishes to emphasize that while no currently available preservative is necessarily 100% effective, at concentrations found in today's vaccines that still contain this preservative, thimerosal meets the requirements for a preservative as set forth by the United States Pharmacopeia (USP) (U.S. Pharmacopeia 2004). Thimerosal in concentrations of 0.001% to 0.01% has been shown to be effective in clearing a broad spectrum of pathogens."

First, we again note that, *by your own admission*, Thimerosal does have established adverse reactions, including "*hypersensitivity*."

Second, as you know and we have established, *in worse-case scenarios*, a "*hypersensitivity*"-type adverse reaction can manifest as anaphylaxis and result in the death of the patient.

Third, you have presented no data, *as required by law* (**21 CFR § 610.15(a)**), to prove that Thimerosal is "sufficiently nontoxic."

The only evidence you have presented are reviews by the IOM and the CDC (Parker et al.) that, *at most*, conclude the evidence is *not* consistent with Thimerosal's causing autism.

When we actually reviewed the studies you sited, a significant number do provide peer-reviewed scientific epidemiological evidence showing a statistically significant increased risk for neurodevelopmental disorders following exposure to the Thimerosal-containing vaccines.

"FDA wishes to comment on your statement. on page P-12 of your petition that at thimerosal's current trace levels it does not meet the accepted USP definition of a preservative. We wish to clarify that the trace levels of thimerosal present in single dose vials of vaccines are residual amounts of this preservative added during manufacture to prevent microbial growth. These trace levels do not constitute a preservative and there is no requirement for a preservative in single dose vials."

While we accept your statements as being valid, we note that, by permitting drug manufacturers to use Thimerosal, a bioaccumulative mercury-based compound that is highly toxic, and a human teratogen, mutagen, carcinogen, immunogen and autoimmunogen, as a process sterilant without requiring proof that, the level in the finished drug product is safe to the point that it conveys no teratogenic, mutagenic, carcinogenic, immunogenic, and/or autoimmunogenic risk to the recipient, *an obvious requirement for optional components (components other than the "active biological moieties")*, you have failed your duty to ensure that the manufacturers prove that their product is "safe" to the extent required to meet the clear requirement *minimums* established in **21 U.S.C. Sec. 351(a)(2)(B)** for finished pharmaceutical products, *in general*, or as set forth in **42 U.S.C. Sec. 262(a)(2)(C)** for biological drug products.

Further, we find that you have failed to establish that allowing these "reduced levels" of Thimerosal to remain in some childhood vaccines without proof that the same formulation without any Thimerosal would have no fewer adverse reactions to the recipient, you have apparently failed to discharge your mandatory duty, as set forth in **42 U.S.C. 300aa-27(a)(2)**, in a manner that complies with said statute.

"In addition, as to your claim on page P-12 of your petition that manufacturers are using thimerosal improperly as an adjuvant, adjuvants are compounds that are added to vaccines to enhance the immune response to the vaccine antigens. Thimerosal does not serve such function and is not used as an adjuvant in U.S. licensed vaccines indicated for pediatric, adolescent, and adult populations."

We respectfully disagree with your unsupported statements here, and refer you to our relevant comments on pages S-R-51 and S-R-52 of this review as well as to the applicable section of page B-15 in **Appendix B** to this review.

Since you have failed to provide any evidence or publications to support your stated views, we must conclude that the **CoMeD** petitioner's evidence-supported views are valid, while your statements appear to be simply unsupportable rhetoric.

doi: 10.1588/medver.2007.04.00145

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

First, since the **CoMeD** petitioners presented other studies that address the consequences of that Thimerosal exposure in cells, animals, and humans, we fail to see the relevance of this heading or the discussion that follows it relative to the overarching reality that the unnecessary use of Thimerosal at any level is "**not proven safe**."

Second, the **CoMeD** reviewers note that some of the cited animal and human studies do report the consequences of the exposures in the timeframes monitored by said studies.

To the extent that the requisite long-term scientifically sound and appropriate toxicological have not been reported or, to our knowledge, conducted, and you have *not* presented any such evidence, we find that that this lack clearly establishes the you have failed to ensure that Thimerosal-preserved vaccines met the clear requirement *minimums* set forth in **21 CFR § 610.15(a)** as required by law (*Berkovitz*[1]) before you can exercise your administrative discretion to license or approve any biological product.

"You state that thimerosal is a neurotoxic compound that should not be permitted in any drug product that is administered to humans or animals unless the manufacturer can prove that the proposed level of the mercury-based compound is safe at 10 times its proposed maximum level and that the medical product cannot safely he used without including this compound or another mercury-containing compound in the formulation (page P-14 of your petition). You have cited articles by *Gasset, et al.*, *Redwood. et al.*, *Slikker, et al., Stajich, et al.*, and *Sager, et al.*, to support this claim (your endnotes 22, 23, 24, 25, and 26)."

Before proceeding, the **CoMeD** reviewers note you do *not* deny that Thimerosal is:

- Neurotoxic at levels below 0.02 ppm, as papers cited in the **CoMeD** petition support, or at levels below 0.001 ppm as Parran *et al*. established in their 2005 paper,[20] or
- A teratogen, mutagen, carcinogen, immunogen and autoimmunogen as the **CoMeD** petition asserts.

"FDA wishes to comment on the findings of these papers, particularly as they relate to your argument. The purpose of the investigation by Gasset, et al. was to evaluate the effect of thimerosal in rats and rabbits when topically applied to the eye and when systemically administered because of observation that ophthalmic medications produce teratogenic effects. No fetal malformations were observed even when given at concentrations approaching the LD_{50} (lethal dose at which 50% of the treated animals die) of these compounds, however, there was increased uterine death in both animal species treated with 2% thimerosal. The authors concluded that the accumulation and potential effects of mercury in maternal and fetal tissues, such as kidney, liver, and brain would require further studies."

Since the **CoMeD** petitioners wrote (on page P-15):

"For example, in 1975, Gasset et al. reported:

'…administration of thimerosal to rabbits shows that a substantial concentration of mercury was present in blood and tissues of the treated animals and their offspring. Thimerosal was found to cross the blood-brain and placenta barriers,'"

it is obvious to the **CoMeD** reviewers that this paper was cited as proof that the mercury administered (with underlining added to highlight the key issues):

- Resulted in "a substantial concentration of mercury was present in blood and tissues of the treated animals and their offspring," and
- Does "cross the blood-brain and placenta barriers."

Since these studies were designed to be "acute toxicity" studies to determine effects and the study periods were mostly very short-term (hours) and, *in no case*, exceeded 48 days, these researchers, *as they should have*, used Thimerosal solutions at levels known to be harmful in humans and, *to lesser degrees*, small animals (*i.e*., rabbit, rat, and mouse) that they could maintain and conveniently study to ensure that they would obtain observable effects and measurable levels of mercury in the samples they tested.

Thus, we find the levels of Thimerosal used were appropriate for the studies conducted and that, because of the limited information collected, the most important issues that this article resolved were the issue of the blood-brain and placental barrier crossing and bioaccumulation in the mothers and the offspring examined.

"We wish to emphasize that in this study, animals were dosed with concentrations of mercury that exceeded by a factor of 100 and 1,000 the amounts generally present in the currently available childhood vaccines that contain trace thimerosal."

doi: 10.1588/medver.2007.04.00145

While your statement is technically correct, the **CoMeD** reviewers that the animals were only dosed with concentrations that are only 1 to 10 times the Thimerosal level in the Thimerosal-preserved vaccines, *including the ineffective inactivated-influenza vaccines*, that are currently being routinely administered to children and pregnant women as well as in almost all of doses of the Thimerosal-preserved vaccines given prior to 2000.

Therefore, we find your statement here is, at best, misleading.

"Thus, the significance of these findings in the context of trace amounts of thimerosal contained in today's pediatric vaccines is unclear."

Since:

- The Thimerosal-preserved influenza vaccines are still approved for administration to pregnant women and babies as young as 6 months of age and
- These studies clearly established that Thimerosal:
  - **a.** crosses the blood-brain and placental barriers and
  - **b.** bioaccumulates in the tissues of adult and fetal animals,

in the context of the Thimerosal-preserved childhood vaccines,

i) ubiquitously used in the U.S. until 2000, *even though the Scandinavian countries and Canada removed them from their general childhood vaccination schedules in the mid-1990s*, and

ii) still used in ineffective inactivated-influenza vaccines approved for use in children and pregnant women,

the significance of the findings cited in the **CoMeD** petition is clear to the **CoMeD** reviewers.

"Redwood, et. al. (2001) assessed the potential impact of mercury from pediatric vaccines given according to the 1999 infant immunization schedule, by estimating hair mercury concentrations utilizing a one-compartment pharmacokinetic model simulating mercury uptake, distribution and elimination."

While we find your statement here is factually more accurate than the petition, which mistakenly stated that the researchers used the 2001 schedule, we find that you missed the key point that this paper highlighted, namely:

> "… study found infants could have been exposed to ***not less than*** 12.5 micrograms (µg) of mercury at birth, 62.5 µg of mercury at 2 months, 50 µg of mercury at 4 months, 62.5 µg of mercury at 6 months, and 50 µg of mercury at approximately 18 months, for a total of ***not less than*** 237.5 µg of mercury during the first 18 months of life, provided: **a)** the infants' vaccinations were all given as scheduled and **b)** the vaccines administered were Thimerosal-containing multi-dose vaccines in every instance."

We find that, using the preceding doses and the EPA "Rfd" of 0.1 µg/kg/day for children, the dose received on each date is a bolus dose that exceeds the EPA "Rfd" by a factor of 10 times the level dosed divided by the child's weight at a given time point.

As "**Reviewer's Table 3**" shows, the dose received is obviously more than 10 times the EPA "Rfd" (0.11 µg/kg/day) at each inoculation age.

This highlights the reality that each dosing significantly mercury poisons the child inoculated for some time after inoculation.

Reviewer's Table 3 Thimerosal "Bolus Dosing": Doses Exceeding EPA RfD

	Child's Age At Inoculation				
	Birth	**2 months**	**4 months**	**6 months**	**18 months**
Dose in µg mercury (Hg)	12.5	62.5	50	62.5	50
Weight in kg (pounds) required for specific dose of 1.0-µg Hg/kg	12.5 (27.6)	62.5 (137.8)	50 (110.2)	62.5 (137.8)	50 (110.2)
5th to 95th percentile weight range for U.S children at a given age[1] (kg)	2.62 – 4.04	4.14 – 5.18	5.52 – 7.60	6.54 – 8.80	"10.1 – 13.5"[2]
Exposure multiple for 5th percentile child	47.7	149.8	90.6	95.6	"49.5"
Exposure multiple for 95th percentile child	37.9	112.0	65.8	71.0	"37.0"
The "Average Child" exposure multiple	30.9	128.6	78.2	83.3	"43.2"

[1] Weights from Geier MR, Geier DA. Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. ***J Am Phys Surg***. 2003; **8**(1): 6-11.

[2] Estimated from 15 months' values.

doi: 10.1588/medver.2007.04.00145

"FDA wishes to comment on the results of these studies. First, infant hair mercury concentrations were estimated, not actually measured. Second, as also noted by the authors, no attempt was made to factor into the model other sources of exposure, e.g., dietary exposure. Other concerns are whether the model used is appropriate for assessing mercury effects in infants from direct exposure, whether a model developed for methyl mercury ingested with food can be applied to an assessment of ethyl mercury injected with vaccines and finally, which of the two scenarios modeled is more valid, i.e., the 'adult excretion model' that assumes mercury excretion rates with a half life of 50 days or the 'no excretion model' that assumes no excretion for the first 6 months of life followed by normal adult rates after this point."

First, we find that, with respect to your initial remarks:

"*FDA wishes to comment on the results of these studies. First, infant hair mercury concentrations were estimated, not actually measured. Second, as also noted by the authors, no attempt was made to factor into the model other sources of exposure, e.g., dietary exposure*,"

these statements accurately reflect what the petition stated in this regard (with underlining added to highlight the key point):

"The authors estimated concentrations of mercury in hair expected to result from the recommended CDC schedule utilizing a one compartment pharmacokinetic model, and found that those modeled mercury concentrations in infants immunized with Thimerosal-preserved 'multi-dose' vaccines were in excess of the Environmental Protection Agency's safety guidelines.

In addition, several modeled peak concentrations within this period were in excess of 4.5 times the EPA limit."

Second, we note that you do *not* dispute that the Thimerosal dosed provided mercury exposures that exceeded, at the time, the EPA "Rfd" of 0.1 µg Hg/kg/day for some period of time and you recently adopted this value as the FDA's level of concern for mercury in drugs given to developing children.

Third, recent studies have clearly shown that that EPA "RfD" should be at least an order of magnitude lower (based on evidence that: **a)** the actual level of exposure in the populations studied was significantly less and **b)** the finding that mercury excretions rates in hair are: **i)** *not* the same in different populations, or **ii)** vary within individuals in a given population [as discussed in Holmes *et al*.]).

Fourth, with respect to your:

"*Other concerns are whether the model used is appropriate for assessing mercury effects in infants from direct exposure, whether a model developed for methyl mercury ingested with food can be applied to an assessment of ethyl mercury injected with vaccines and finally, which of the two scenarios modeled is more valid, i.e., the 'adult excretion model' that assumes mercury excretion rates with a half life of 50 days or the 'no excretion model' that assumes no excretion for the first 6 months of life followed by normal adult rates after this point*,"

we note that, though the half-life times reported for hair have *not* been confirmed, the paper by Burbacher *et al.* [41] has shown that, *for changes in blood levels following mercury-compound dosings in the baby monkey groups studied*, the pattern for ingested methylmercury hydroxide is similar to the pattern projected for the authors' "no excretion" model (**see footnote 67**'s **Figure 2**), while the pattern for the injected Thimerosal is similar to the pattern projected for the authors' "adult excretion" model (**see footnote 67**'s **Figure 5**).

Though Burbacher *et al*. (2005) focused on the differences seen as differences in the mercury-based compound dosed, we find that the differences Burbacher *et al*. observed are more probably attributable to the differences in the mode of administration (ingestion [oral gavage] *versus* injection) than the differences in the compound tested (methylmercury hydroxide *versus* Thimerosal).

Based on Burbacher *et al*., the authors' "adult excretion" model seems appropriate for clearance of Thimerosal-derived mercury from blood, while, for Thimerosal-derived "inorganic mercury" found in the brains of the baby monkeys injected with Thimerosal, the Thimerosal-dosed data clearly indicate that a "no excretion for greater than 120 days after dosing is stopped" model is appropriate.

We think that the preceding discussion has adequately addressed the issue of which type of model is appropriate and where each type of model is appropriate when it comes to modeling the decay of the mercury level in blood in primate circulatory systems or primate brains.

"*Slikker, et al. (2000)* discussed thimerosal as a preservative in vaccines in the context of therapeutic agents presenting special challenges to risk assessment because they may present both risk and benefit to human health. He referred to data showing that thimerosal crosses the blood-brain and placental barriers, resulting in accumulation of mercury in the brain. However, he stressed that therapeutic agents represent both risks and benefits to human health and that therefore, there is a need to further study this important ingredient (i.e., thimerosal) with regard to both benefits, and potential associated risk."

doi: 10.1588/medver.2007.04.00145

First, the **CoMeD** reviewers note that this reference was used to show that, in 2000, the FDA was well aware "*thimerosal crosses the blood-brain and placental barriers, resulting in accumulation of mercury in the brain*" since the **CoMeD** petitioners wrote:

> "Similarly, in 2000, Slikker" **petition endnote 24**" from the FDA stated,
> 'Thimerosal (sodium ethyl mercurithiosalicylate) crosses the blood-brain and placental barriers and results in appreciable mercury content in tissues including the brain,'"

in the overarching context of "safety not proven."

Moreover, we observe you report, "*there is a need to further study this important ingredient (i.e., thimerosal) with regard to both benefits, and potential associated risk*," but that you have *knowingly* failed to follow the advice given and perform the *in-depth* acute, chronic, reproductive, and long-term toxicity of Thimerosal required to *properly* assess the "*risk*" or, *as required by law* (**21 CFR 610.15(a)**) *before the licensing/approval of any Thimerosal-preserved vaccine*, require the vaccine makers to perform the requisite toxicity studies.

In that regard, in spite of having been noticed about this legal requirement by the **CoMeD** petitioners in 2004, you have continued to license new Thimerosal-preserved vaccine formulations, including, on Thursday, 5 October 2006, FluLaval®, a Thimerosal-preserved (0.01%) inactivated-influenza-virus vaccine, without, *as far as we can ascertain*, requiring the manufacturer to conduct said toxicity studies to prove safety (a prerequisite for assessing "*risk*") and in spite of a published study[20] clearly establishing, *based on published U.S. government data*, that inactivated-influenza-virus vaccines are *not* effective in preventing: **a)** those inoculated from contracting influenza or **b)** the spread of influenza in the population.

"*Stajich, et al. (1999)* measured total mercury levels before and after administration of hepatitis B vaccine (Engerix®) to preterm (n=15) and term (n=5) infants. Even though authors were concerned about increasing the neurologic risk for preterm infants as a result of mercury exposure, **they state that there is no information to suggest a causal link with immunizations.** The authors also mentioned that at that time, namely 1999, few alternatives were available to infants born to hepatitis B-infected mothers because a thimerosal-preservative-free hepatitis B vaccine was not yet available. Since then, two hepatitis B vaccines containing either no thimerosal or trace amounts of thimerosal from the manufacturing process have been licensed, and are now the only hepatitis B vaccines available in the United States to all age groups.

First, with respect to your, "*Stajich, et al. (1999) measured total mercury levels before and after administration of hepatitis B vaccine (Engerix®) to preterm (n=15) and term (n=5) infants. Even though authors were concerned about increasing the neurologic risk for preterm infants as a result of mercury exposure, **they state that there is no information to suggest a causal link with immunizations***," we note that this is again an implicit admission on your part that you have failed:

- *After December 22, 1987*, to comply with the mandate imposed upon you by **42 U.S.C. Sec. 300aa-27(a)(2)** or
- *Since November 20, 1973*,to enforce the proof of "sufficiently nontoxic" requirement set forth in **21 CFR § 610.15(a)**,

even though required to do so by the U.S. Supreme Court's 1988 unanimous decision in *Berkovitz*[1].

Moreover, we find it is equally true that **there is no scientific proof that there is no risk that Thimerosal at the preservative levels causes significant neurological injury in some children**.

Second, we find your need to state, "*The authors also mentioned that at that time, namely 1999, few alternatives were available to infants born to hepatitis B-infected mothers because a thimerosal-preservative-free hepatitis B vaccine was not yet available*," interesting because, *as you fail to note*, though less than 0.002%[65] of the U.S. infants born each year are reportedly "*born to hepatitis B-infected mothers*," you persist in recommending that all infants be inoculated for hepatitis B although, *as far as we can ascertain*, that inoculation, as you know, conveys virtually no immunity to the infants vaccinated at birth.

Given the fact that almost no babies are at risk of contracting hepatitis B at birth and the hepatitis B vaccine administered at birth is *not* effective in immunizing them from getting hepatic B, the **CoMeD** reviewers are compelled to ask you:

"Given:

---

[65] http://www.trans4mind.com/world-psychology/cryheart.html. Cry of the Heart The Medical Terror of Vaccinations by Mark Sircus, Chapter 1, "In 1996, only 54 cases of the disease were reported to the Centers for Disease Control and Prevention (CDC) in the 0 to 1 age group. There were about 3.9 million births that year, so the observed incidence of hepatitis B in the 0 to 1 age group was just 0.001 percent." – Incidence rate < 0.0014%.

doi: 10.1588/medver.2007.04.00145

- There is no universal risk to newborns contracting hepatitis B,
- An effective rapid hepatitis B test exists to identify "*hepatitis B-infected mothers*," and
- A hepatitis B immune globulin product is available in sufficient quantities to protect those '*infants born to hepatitis B-infected mothers*' from getting hepatitis B, and
- Hepatitis B vaccine provides virtually no protection to newborns,

why, *other than to fatten the manufacturers' and the healthcare providers' wallets*, have you have recommended giving the hepatitis B vaccine to all newborns?"

"What are you concealing from the American public about the current hepatitis B vaccines?"

"What is the real reason for your recommendation?

Third, we find that your:

"*Since then, two hepatitis B vaccines containing either no thimerosal or trace amounts of thimerosal from the manufacturing process have been licensed, and are now the only hepatitis B vaccines available in the United States to all age groups*,"

conveniently ignores the tens of million children who were injected with the Thimerosal-preserved hepatitis B vaccine and the hundreds of thousands that may have been harmed by their birthday dose of this Thimerosal-preserved vaccine to the point that they exhibited one or more of the clinical symptoms of sub-acute mercury-poisoning.

Turning to the **CoMeD** petition, where the **CoMeD** petitioners wrote:

"Additionally, Stajich et al." **petition endnote 25** "have examined total mercury levels before and after the administration of hepatitis B vaccine in 15 pre-term and 5 term infants.

In 2000, these authors reported that there were statistically significant increased levels of mercury in the blood 48 to 72 hours following hepatitis B immunization in both pre-term (relative increase = 13.5, $p < 0.01$) and term (relative increase = 56, $p < 0.01$) infants."

the **CoMeD** reviewers note that even though this data was for samples taken 2 to 4 days after inoculation, the levels of mercury in the infants' blood streams was still *significantly* elevated.

Since you began recommending giving inactivated-flu vaccines to pregnant women in 2002 and most doses of those vaccines contain a preservative level of Thimerosal, we find that the recent (2006) news reports of a significant increase in the percentage of pre-term babies delivered are probably connected to the mostly Thimerosal-preserved influenza vaccines their mothers have received because:

- the level of mercury in U.S. air, food, and water has *not* significantly increased,
- pregnant women have been warned of the risk of mercury in fish and reduced their fish consumption, and
- the use of mercury in dentistry has actually declined,

thus, reducing the fetus' mercury-poisoning risk contributions from mercury from these other sources.

Finally, we observe that, in view of:

- The preceding anecdotal evidence in humans,
- Evidence of a causal link between "mercury exposure *in utero*" and "birth prematurity" in animals,[66]
- The fact that some American mothers who gave birth in the time period of the study by Stajich *et al*. received Thimerosal-preserved Rho(D) products, and
- This article's reporting that the levels of mercury in the blood of the pre-term babies was reported as 0.54 ± 0.79 ppb versus 0.04 ± 0.09 ppb for the term infant,

the **CoMeD** reviewers again question:

- Your admitted failure to require scientifically sound and appropriate multi-generational reproductive studies of Thimerosal at 0.1-, 1.0-, 10.0-, and 100- times the maximum preservative levels in vaccines using an animal model, like the SJL/J mouse or the rat strain used in the reference Goncharuk study, [66] that is susceptible to the toxic effects of Thimerosal before approving any Thimerosal-preserved vaccine for administration – much less approving an ineffective vaccine, [20] and
- Your general failure to require proof of safety as mandated (**21 CFR § 610.15(a)**)

[66] Goncharuk GA. Experimental investigations of the effect of organomercury pesticides on generative functions and on progeny. ***Hyg. Sanit***. 1971; **36**: 40-43.

doi: 10.1588/medver.2007.04.00145

"Summary results presented by *Dr. Polly Sager (2004)* at the IOM meeting in February 2004 (cited in your endnote 26) are now published by *Burbacher, et al.* FDA notes that in this study infant monkeys were administered thimerosal mixed with thimerosal-free vaccines to yield a final concentration of 4, 8, or 20 µg/ml, depending on the vaccine and the age of the monkey. The total dose of mercury administered was 20 µg/kg mercury administered on day 0, 7, 14, and 21 days of age. According to the authors, this dose was chosen based on the range of estimated doses received by human infants receiving vaccines during the first 6 months of life."

The **CoMeD** reviewers do *not* dispute the factual information stated concerning the Thimerosal arm of the published study by Burbacher *et al*.

"FDA wishes to emphasize that the cumulative amount of mercury from vaccines that an infant less than 6 months of age can now be exposed to is ‹3 µg, or approximately 15 µg if a thimerosal-containing influenza vaccine was used at 6 months of age."

First, using the current recommended vaccination schedule for children and pregnant women, we find that your statement is *not* accurate.

Factually, including the 25-µg dose given to pregnant women, "*the cumulative amount of mercury from vaccines that an infant less than 6 months of age*" can now be exposed to is ‹28 µg, "*or approximately*" 40 µg "*if a*" "Thimerosal-preserved" "*influenza vaccine was used at 6 months of age*," or approximately 53 µg, if, *as the current national immunization schedule suggests*, a Thimerosal-preserved influenza vaccine was again used at 7 months.

Thus, you have apparently *knowingly* underestimated the nominal maximum exposure in the earliest period of life for babies born after 2005 by a factor of about 9 (before 6 months), and factor of about 3 at 6 months. [**Note:** Prior to 2000, the comparable nominal vaccine-mercury exposure levels were 125 µg before 6 months and 187.5 µg at 7 months. Including 1 fetal generic-Rho(D) or 2 brand-Rho(D) exposures and a single flu shot, the maximum exposures increase to 175 µg before 6 months and 237.5 µg in the 6–7-months period.]

Second, we find you failed to address the reality that the cumulative exposure level given to the baby monkeys was significantly less than the cumulative exposure a human child who received *in utero* exposure to Thimerosal from Thimerosal-preserved Rho(D) serum products and was, *after birth*, inoculated with all Thimerosal-preserved vaccines as recommended in the childhood immunization schedule would have received by two years of age.

Third, we find that the cumulative exposure level used was lower than a child would have received by 2 years of age and note that, *contrary to the usual design of toxicity assessment*, the study did *not*, as it should have, include a 10-X exposure arm to ensure that toxic effects, *if any*, might be observed because the study period was much shorter than the "two to five" years needed to see significant levels of clinical harm because mercury is known to be a insidious poison for which, *at sub-acute dosing levels*, the onset of clinical symptoms may be delayed for considerable periods.

"These levels are significantly lower than the one used in the study by Burbacher, et al."

We note that, *after correcting your values appropriately*, the current levels of Thimerosal were somewhat, *not significantly*, lower than the levels used in the study by Burbacher, *et al*.

We also note that you have knowingly failed to address the tens of millions of children, born before 2000, whose cumulative mercury exposure easily exceeded that used by Burbacher *et al*. or, *if your recommended vaccination schedule for children and pregnant women is followed*, the cumulative dose current children could receive from before birth to age 5 if continually dosed with a Thimerosal-preserved influenza vaccine – vaccines that are, *based on their in-use history*,[20] clearly ineffective.

"Furthermore, we note that the results of this study do not provide evidence that trace amounts of thimerosal contained in today's childhood vaccines are linked to neuro-developmental effects.

First, the **CoMeD** reviewers can only agree that the reported "*results of this study do not provide evidence that trace amounts of thimerosal contained in today's childhood vaccines are linked to neuro-developmental effects,"* because we have been unable to review all of the documentation and ascertain what informational items, *if any*, were withheld from publication.

As we now observe, your noted "finding" supports, *among other things*, the **CoMeD** petitioners' contention that the safety of Thimerosal has *not* been proven.

In fact, we are at a loss to understand what, if anything, this study was actually designed to assess:

doi: 10.1588/medver.2007.04.00145

- If the study were designed to validly assess the toxic effects of Thimerosal, then its failure to dose the test animals at higher levels, 10X or 10X and 100X the vaccine levels and follow the animals for longer periods of time (12- to 24- months) rendered it inappropriate for that use.
- If the study were designed to validly assess the differences in the distribution of mercury from methylmercury hydroxide and Thimerosal in the bodies of the test subjects, then the study is defective on two counts because the study failed:
  1. To add equivalent amounts of methylmercury hydroxide (on a mercury basis) to the Thimerosal-free vaccine matrix it added the Thimerosal to (instead, it dissolved the methylmercury hydroxide in water), and
  2. To use the same route of administration for both compounds (the Thimerosal solutions were injected; the methylmercury hydroxide solutions were orally force fed [gavaged]).
- If the study were designed to assess mercury clearance from the test subjects, then radiolabeled or isotopically labeled compounds should have been used and the animals' feces and urine collected and analyzed to show the rate that the compounds cleared the animals but, *if these studies were done*, they were *not* reported.
- If the goal were to assess evidence of toxicological damage to the brain or other organ, then the researchers should have appropriately sectioned and stained the animals' organs and microscopically examined the tissues to see how the organs of the test subjects differed from those of the controls, but again such studies were *not* reported.

Based on the preceding, we find that the study by Burbacher *et al*. seems to have been *deliberately* designed to confound the factors so that, *whatever the findings*, the confounding factors could be used to undermine said findings – and, in that, the study succeeded.

Again, we find the **CoMeD** petitioners proffered this study as evidence of accumulation of Thimerosal-derived "mercury" in the brain *not* knowing, because Sager's slides failed to address "inorganic mercury" (because the "28-day" half-life reported for "mercury" in the brain was the half-life of the "organic mercury") that, *as the published study* (published in August of 2005, a year after the **CoMeD** petitioners submitted their petition) *reported*, a significant portion of the Thimerosal dosed was ending up in the brain in the form of an "inorganic mercury" that had a half-life longer than their study could accurately measure (they reported > 120 days; but large-animal toxicity studies using alkyl mercurials have reported "inorganic mercury" half-lives in the range of 20 to 30 years.]

Thus, Burbacher *et al*. only showed that a significant portion of the injected Thimerosal ended up 48 days later as "inorganic mercury" in the subjects' brains, where, *based on large-animal studies*, it has a decades-long half-life during which it continues to mercury-poison the brain.

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

Contrary to your unsubstantiated (by documented study or recognized scientific reference text), the **CoMeD** reviewers find that the studies cited by the petitioners:

- Are valid science and
- Do support eliminating all Thimerosal from all products.

However, notwithstanding that finding, the **CoMeD** reviewers note that under *Berkovitz*[1]:

- Conformance to the explicit requirements of **21 CFR § 610.15(a)** and/or **42 U.S.C. Sec. 300aa-27(a)(2)** would, at a minimum, require you to revoke the approval of all the current Thimerosal-containing or other mercury-based additive in biological products that may be directly or indirectly administered to any child, defined as from the human from conception until the person reaches 18 years of age and
- Conformance to the implicit "prove safe" requirements of **21 U.S.C. Sec. 351(a)(2)(B)** and **42 U.S.C. 262(a)(2)(A)** would require you to remove all other Thimerosal- and other-mercury- containing drugs from the market,

unless, *because Thimerosal is not only toxic to cells below 0.001 ppm but is also a proven teratogen, carcinogen, mutagen, immunogen, and autoimmunogen at levels below 1 ppm*, the manufacturers have proven:

- No other compound can be used, and
- The product is "safe" for administration to mercury-poisoning-susceptible individuals (a group that is known to exist) by conducting the appropriate scientifically sound toxicological studies,

requirements that, *given the sub-ppb toxicity of Thimerosal*, we find *cannot* be met in any scientifically sound and appropriate toxicity study using an appropriate "mercury-poisoning-susceptible animal" model.

doi: 10.1588/medver.2007.04.00145

"You state that FDA has not followed recommendations by researchers calling for an end to adding any amount of thimerosal to vaccine and related products (pages P-30 and P-31 of your petition). You cite articles by *Nelson and Gottshall (1967), Heyworth and Truelove (1979), Forstrom (1980), Kravchenko, et al, (1983), Winship (1986), Cox and Forsyth (1988) and Seal, et al. (1991), van't Veen (2001), and Schumm, et a1. (2002)* (refer to endnotes 42-50)."

We find that you have correctly stated the issue the **CoMeD** petitioners raised and note that each of the listed references cited did make the statements that clearly support the recommendation stated.

"FDA has reviewed the references and notes the following: *Nelson and Gottshall (1967)* conclude that there are no data to suggest that thimerosal-preserved pertussis vaccines which show a greater toxicity in mice than unpreserved vaccines also have a greater toxicity in man. In addition, we observe that the mice (14-16 g) received doses of 70 µg thimerosal, e.g., 4.6 mg/kg thimerosal, which is approximately 4620-fold the dose of mercury generally contained in today's childhood vaccines with trace amounts of mercury."

First, we note that your comments failed to addressed issue raised by the petitioners who wrote:

> "In 1967, Nelson and Gottshall from the Division of Biologic Products, Bureau of Laboratories, Michigan Department of Public Health published:
>
> > 'Pertussis vaccines preserved with 0.01% Merthiolate are more toxic for mice than unpreserved vaccines prepared from the same parent concentrate and containing the same number of organisms… An increase in mortality was observed when Merthiolate was injected separately, before or after an unpreserved saline suspension of pertussis vaccine.'"

since the excess toxicity observed was proven to be caused by the Merthiolate (a/k/a Thimerosal) and the level of Thimerosal, "0.01%," the same level found in most Thimerosal-preserved vaccines.

At a minimum, this article clearly establishes that 0.01% Thimerosal in a vaccine formulation, or in saline, was significantly toxic to mice at the dose administered shortly after the dose was administered.

Further, we note: **a)** your assertion, "*there are no data to suggest that thimerosal-preserved pertussis vaccines which show a greater toxicity in mice than unpreserved vaccines also have a greater toxicity in man*," fails to address the legal issues raised in the **CoMeD** citizen petition, and **b)** there is also no data to suggest that Thimerosal-preserved pertussis vaccines which show a greater toxicity in mice than unpreserved vaccines do *not* also have a greater toxicity in man.

Returning to the key issues raised by the **CoMeD** petitioners, *since you have knowingly continued to license/approve Thimerosal-preserved childhood vaccines*, we note that the dose administered was approximately 46-fold the dose of mercury generally contained in the Thimerosal-preserved childhood vaccines you have continued to license/approve – the very vaccines the **CoMeD** petitioners seek to remove from the market unless their manufacturers can prove their vaccines meet the clear "sufficiently nontoxic" requirement of **21 CFR § 610.15(a)** and, *for childhood vaccines*, you can prove that removing the Thimerosal does *not* reduce the adverse reactions caused by the Thimerosal-preserved vaccine under **42 U.S.C. Sec. 300aa-27(a)(2)**.

Hopefully, when you do finally address the key **CoMeD** petition issues:

- "… sufficiently nontoxic …" as set forth in **21 CFR § 610.15(a)**, and
- "Mandate for safer childhood vaccines" as set forth in **42 U.S.C. 300aa-27(a)(2)**

the **CoMeD** reviewers trust that you will then do so in a manner that complies with the legal limitations placed on your administrative discretion by *Berkovitz*.[1]

"*Heyworth. et al. (1979)* measured the cytotoxic effects of anti-lymphocytic globulin on peripheral blood mononuclear cells (PBMC), which are white blood cells), tonsil lymphocytes and blood cells in an in vitro system measuring ^{51}Cr release from labeled cells. Because of data in the literature on binding of merthiolate to sulfhydryl (SH) groups of proteins, the authors suggest that if thimerosal binds to horse immunoglobulin, it may reach a toxic level in the region of lymphoid cells. While data provide further evidence about the known in vitro cytotoxic effects of mercury, no direct evidence was provided in this paper that would support the conclusion of the authors."

The **CoMeD** reviewers find you failed to support your "*no direct evidence was provided in this paper that would support the conclusion of the authors*" with any scientific evidence that contradicted the researchers' findings or substantiated your objection to the authors' conclusion.

Based on this finding, we must conclude that your objection lacks substance.

Therefore, we again support the authors' science-based conclusion, first published in 1979:

doi: 10.1588/medver.2007.04.00145

"We should like to suggest that merthiolate should now be regarded as an inappropriate preservative for anti-lymphocytic globulin preparations and other materials which are intended for administration to human subjects."

Next, we note that you failed to address the recommendations published in 1980 by Forstrom et al. (petition endnote 44, "Lars Forstrom, M. Hannuksela, Merja Kousa and E. Lehmuskallio, 'Merthiolate hypersensitivity and vaccination,' ***Contact Dermatitis***, **6**, pages 241-245 (1980)"), who studied humans, in which these researchers clearly stated (with underlining added to highlight the issue):

"…reactions can be expected in such a high percentage of merthiolate-sensitive persons that merthiolate in vaccines should be replaced by another antibacterial agent."

Clearly, you did *not* address this article because it clearly shows:

- Merthiolate (another name for Thimerosal) in vaccines produces adverse reactions in humans,
- That these researchers warned you to remove it from vaccines in 1980,
- You ignored their warning, and
- Because the requirement set forth in **21 CFR § 610.15(a)** had become law in 1973,

you were *knowingly* permitting vaccine makers to *knowingly* ignore this legally binding regulation's "sufficiently nontoxic" requirement.

"*Kravchenko, et at. (1983)* evaluated toxic properties in medical biological preparations by the degree of cell damage using an in vitro system of an L132 continuous cell line. The authors conclude that thimerosal has cytotoxic effects on in vitro cell cultures and suggest that the use of thimerosal in biological preparations, especially those intended for children, is inadmissible. As stated above (refer to item IIa), FDA acknowledges that mercurial compounds. when applied directly to in vitro cell systems, can cause dose-dependent cytotoxic effects; however, these data do not prove that thimerosal causes harm to the human body."

First, we again observe:

- The burden of proof:
  - Is to prove safety,
  - Is yours and the vaccine makers, and
- You have knowingly failed to require the requisite proof of safety under **21 CFR § 610.15(a)** as you should have before licensing or continuing to license any Thimerosal-preserved vaccine or other biological product.

Second, you again have failed to provide any scientific evidence or references to support your dismissal of *in vitro* studies showing significant toxicity that are supportive of the petitioners' request.

Third, these data do *not* provide any evidence that Thimerosal is *not* harmful to the human body.

Given the preceding realities and having reviewed the subsequent literature, we find that this 1983 publication by Kravchenko *et al*. properly recommended:

"… the use of thimerosal for the preservation of medical biological preparations, especially those intended for children, is inadmissible."

"*Winship, et al. (1986)* reviewed the use of organic mercury compounds, sources of exposure, absorption, distribution, biotransformation, excretion, toxicology, and treatment and states that multi-dose vaccines and allergy-testing extracts containing 0.01% thimerosal may present problems occasionally in practice. Furthermore, the studies by *Farstroem, et at. (1980), Van't Veen (2001), Cox and Forsyth (1988) and Seal, et al. (1991)*, are mainly concerned with hypersensitivity reactions to thimerosal and primary sensitization to thimerosal. The general conclusion was that overall exposure to thimerosal should be reduced and in particular the exposure via vaccines and immunoglobulin to children and young adults should be eliminated. FDA must reemphasize that thimerosal has been removed or significantly reduced from currently licensed vaccines indicated for the pediatric, adolescent, as well as the adult population."

First, we find you have misrepresented the general conclusions reached by the authors of the articles referenced here because overall, they recommended Thimerosal should be removed from vaccines and other biological products (*e.g.*, immunoglobulins), *not* simply "*reduced*" as you have stated:

- In 1986, Winship reported :

  "Multi-dose vaccines and allergy-testing extracts contain a mercurial preservative, usually 0.01% thimerosal, and may present problems occasionally in practice. It is, therefore, now accepted that multi-

doi: 10.1588/medver.2007.04.00145

dose injection preparations are undesirable and that preservatives should not be present in unit-dose preparations" –

simplistically, Winship was recommending:

- Stop using multi-dose preparations that contain Thimerosal as a preservative, and
- Remove the Thimerosal from unit-dose preparations, which at the time contained preservative levels of Thimerosal.

- Similarly, in 1988, Cox and Forsyth (petition endnote 47, "Neil H. Cox and Angela Forsyth, 'Thiomersal allergy and vaccination reactions,' ***Contact Dermatitis***, **18**, pages 229-233") urged:

  "However, severe reactions to thiomersal demonstrate a need for vaccines with an alternative preservative."

  Since Thiomersal is another name for Thimerosal, these researchers "need for vaccines with an alternative preservative" recommendation is again a recommendation to remove Thimerosal and replace it with another preservative system.

  In addition, these researchers were reporting finding "severe reactions" to Thimerosal in humans – clearly indicating Thimerosal toxicity to humans at preservative levels (0.001% to 0.01%).

  This article is important because **42 U.S.C. Sec 300aa-27(a)(2)**, which became effective in December of 1987, mandated your reducing adverse reactions in childhood vaccines and, *based on this paper*, you knowingly ignore this mandate, have continued to do so, and are continuing to license Thimerosal-preserved childhood vaccines to this day.

  Further, even though their research findings clearly established that Thimerosal-preserved vaccines are *not* "sufficiently nontoxic" as required by **21 CFR § 610.15(a)**, you have knowingly continued to ignore this clear law until the present (licensing/approving the Thimerosal-preserved FluLaval vaccine on October 5, 2006).

  Finally In addition, this article is important because on June 13, 1988 the US Supreme Court unanimously ruled found in *Berkovitz*[1] that you do *not* have any administrative discretion to ignore any clear requirement set forth in any enacted policy, law or statute – and yet you have *knowingly* acted in contempt of that court's decision from that day until the present.

- In 1991, Seal *et al*. commented in the ***Lancet*** (petition endnote 48 "David Seal, Linda Ficker, Peter Wright and Victor Andrews, "The case against thiomersal," ***The Lancet***, **338**, pages 315-316 (August 3, 1991)"):

  "Thiomersal is a weak antibacterial agent that is rapidly broken down to products, including ethyl mercury residues, which are neurotoxic. Its role as a preservative in vaccines has been questioned, and the pharmaceutical industry considers its use as historical."

  The **CoMeD** reviewers observe that you did *not* address or dispute the neurotoxicity of Thimerosal or that the researchers' "industry considers its use as historical" – clearly meaning obsolete.

  Since, in 1991, these researchers found that, at vaccine levels, Thimerosal is neurotoxic to humans, you again should have required all Thimerosal-preserved biological products to switch to an alternate preservative system unless the product maker had and submitted scientifically sound and appropriate toxicological studies to prove their product formulation was "sufficiently non toxic" (**21 CFR § 610.15(a)**) or, *for vaccines approved for administration to children*, the removal of Thimerosal would *not* have reduced the adverse reactions being reported.

  But you knowingly continued to ignore *Berkovitz*[1] and the applicable legal and statutory requirements the **CoMeD** petitioners have repeatedly cited.

- In 2001, van't Veen (petition endnote 49, "Albert-Jan van't Veen, 'Vaccines Without Thiomersal Why So Necessary, Why So Long Coming?,' ***Drugs***, **61**(5), pages 565-572") stated (with underlining added to highlight the key issue):

  "The very low thiomersal concentrations in pharmacological and biological products are relatively non-toxic, but probably not in utero and during the first 6 months of life. The developing brain of the fetus is most susceptible to thiomersal and, therefore, women of childbearing age, in particular, should not receive thiomersal-containing products."

  Here the author was recommending the removal of a particular groups of individuals, pregnant women and children 6 months of age and younger, should be removed from Thimerosal-containing products.

  Yet, we find that you ignored this author's recommendation and the supporting science and the applicable laws and statutes.

  In 2002, you began recommending that pregnant women and children 6-months to 23-months of age during the US influenza season be given inactivated flu vaccines, including the Thimerosal-preserved vaccines – increasing the risk of children to adverse reactions (a knowing violation of **42 U.S.C. 300aa-27(a)(2)**) and, *based on this research report*, knowingly violating **21 CFR § 610.15(a)** since you had no proof that Thimerosal in the Thimerosal-preserved vaccine was "sufficiently nontoxic so that the amount present in the recommended dose of

doi: 10.1588/medver.2007.04.00145

the product will not be toxic to the recipient" – in this case, to the fetus who is exposed to up to 50 µg of Thimerosal when the fetus' mother is inoculated with a Thimerosal-preserved flu vaccine.

We further find that you have continued to illegally permit Thimerosal-preserved flu shots to be given to pregnant women without proof of safety to the fetus in spite of the recent article by Ayoub and Yazbak[22] who clearly established that you had no scientifically sound and appropriate proof of safety and there was a body of evidence and information pointing to fetal harm.

Based on our review of these references and the applicable laws and statutes, we find that the authors in the majority of these papers clearly recommended removing Thimerosal from vaccines and, since, under *Berkovitz*,[1] you have no discretion *not* to: **a)** comply with (**42 U.S.C. Sec.300aa-27(a)(2)**), or **b)** require compliance by the manufacturers with (**21 CFR § 610.15(a)**), the law, you should have removed all licensed/approved Thimerosal-preserved vaccines from the market and stopped licensing/approving Thimerosal-preserved vaccines in 1973 or, after *Berkovitz*,[1] no later than mid-1988.

Finally, given the clear adverse reactions in "reduced Thimerosal" vaccines, you should have amended the licenses/approvals of all Thimerosal-containing vaccines to proscribe their being administered to children and pregnant women (whose fetuses are exposed to Thimerosal when their mothers are inoculated) under **42 U.S.C. Sec. 300aa-27(a)(2)**.

However, we again note that you have continued to ignore *Berkovitz*[1] and the applicable requirement minimums established by law when it comes to Thimerosal-containing drugs.

"*Schumm, et al. (2002)* assessed the effects of anthrax vaccination on the long-term health of U.S. male and female Reserve Component Gulf War veterans. FDA notes that this author's interpretations are speculative and no data were presented that would link mercury contained in the vaccine(s) administered to 'adverse long-term outcomes' experienced by the Gulf War Veterans."

The **CoMeD** reviewers observe that though you are entitled to your views of this paper, you are *not* entitled to ignore their recommendations unless you have proof of safety that overcomes their recommendations.

Since you have presented no proof to substantiate your claims, the **CoMeD** reviewers must accept the 2002 recommendations of Schumm et al. (petitioners' endnote 50, "Walter R. Schumm, Earl J. Reppert, Anthony P. Jurich, Stephan R. Bollman, Farrell J. Webb, Carlos S. Castelo, James C. Stever, Diane Sanders, Gabriele N. Bonjour, Janet R. Crow, Carol J. Fink, Jeanne F. Lash, Beverlyn F. Cay Brown, Carolyn A. Hall, Barbara L. Owens, Michelle Krehbiel, Liang-Yu Deng and Mark Kaufman, "Self-Reported Changes In Subjective Health And Anthrax Vaccination As Reported By Over 900 Persian Gulf War Era Veterans," Psychological Reports, 90, pages 639-653"):

"We also recommend that safer alternatives to thimerosal (a mercury sodium salt, 50% mercury) be used to preserve all vaccines."

The **CoMeD** reviewers find that, as asserted by the **CoMeD** petitioners, the "*FDA has not followed recommendations by researchers calling for an end to adding any amount of*" Thimerosal to vaccines and other biological products.

Further, many of the cited articles clearly provide evidence of Thimerosal's toxicity.

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

Since you have failed to provide any scientific evidence or studies to support your claims, the **CoMeD** reviewers have rejected them since they are unsubstantiated.

In addition, we find your heading's, "*The Methyl Mercury Studies Cited …*," is, ***at best***, ***knowingly*** misleading because the studies cited studied both "*ethyl mercury*" compounds and "*methyl mercury*" compounds as your own statements in the text admit.

Likewise, we find your heading's, "*… Studies Cited are … Inapplicable to Human Vaccines*," is also at odds with factual reality because:

- Thimerosal, also known as "ethyl mercury thiosalcylate, sodium salt," is an "*ethyl mercury*" compound,
- In the aqueous saline carrier used for the formulation of Thimerosal-containing vaccines, Thimerosal is known to be partially solvolytically converted into ethyl mercury chloride and ethyl mercury hydroxide, and

doi: 10.1588/medver.2007.04.00145

- After injection, the human body initially metabolizes the remaining Thimerosal in the injected vaccine dose into ethyl mercury chloride and ethyl mercury hydroxide.

"You have cited publications by *Tryphonas, et al.*, *Fagan. et al.*, and *Magos, et al.* (endnotes 51, 52, 53) to compare the relative toxicities of ethyl mercury and methyl mercury."

Technically, the **CoMeD** reviewers only agree that the **CoMeD** petitioners cited these articles to compare the "*toxicities of ethyl mercury and methyl mercury*."

"*Tryphona, et al.* conclude that alkyl mercury compounds, if fed at low concentrations for long periods, were poisonous to swine. The authors were concerned with public health implications, especially when meat, liver, etc., of poisoned pigs are consumed by people."

Reviewing the petitioners´ statements, yours, and the article cited, we find that your narrative is, at best, problematic.

Factually, the periods of time were only up to 60 days for the methyl mercury compound ("MMD") and up to 90 days for the ethyl mercury compound ("EMC") tested. [**Note:** Reviewing the treatment period data, we find that, at the high-dose, the treatment periods, *for those pigs not slaughtered early*, were 41 to 46 days for the "MMD" treatment and 30 days for the "EMC" treatment. At the mid-dose level, the treatment periods, *for those pigs not slaughtered early*, were 60 days for the "MMD" treatment and 75 to 90 days for the "EMC" treatment.]

Second, in the treatment groups, the dosages used were equivalent to 0.19 (group I), 0.38(group II) and 0.76 mg Hg/kg per day (group III) or 0.19 ppm, 0.38 ppm, and 0.76 ppm because the goal of the study was to induce clinical mercury poisoning.

Third, the investigators found that the EMC compound was more toxic than the MMD compound as their "Table 2—Mean, Minimal and Maximal Values in Days for …" clearly showed.

For example, *for the group II pigs*, no visible clinical signs were seen for the MMD compound while the EMC-treated group exhibited the following pattern:

	Day of Onset of Clinical Symptoms
Clinical Signs	**Average (Minimum- Maximum)**
Anorexia	12 (12-12)
Retarded growth rate	16 (14-18)
Incoordination	52 (49-56)
Aimless walking	52 (49-56)
Blindness	52 (49-56)
Empty mastication	51 (51-51)
Flaccid abdominal musculature	52 (49-56)
Negative weight balance	58 (53-64)
Tremor	47 (44-50)
Peddling Movements	66 (60-71)
Comatose	67 (61-73)
Death	70 (64-75)

Fourth, there was considerable individual variability among the pigs, as the authors stated:

"The importance of susceptibility of the individual animal to organomercurial poisoning became apparent in group II pigs in which, within the time period studied, 3 pigs developed severe lesions and clinical signs, 3 had clinically silent lesions, and 2 remained unaffected."

However, while true, we find that your, "*The authors were concerned with public health implications, especially when meat, liver, etc., of poisoned pigs are consumed by people*," is of no relevance to the petition or the issues it raises.

Thus, the **CoMeD** reviewers find that the petition did *not* overstate this paper's findings when the paper stated:

"In some cases, it was even determined that ethyl mercury was more toxic than methyl mercury.

For example, in the early 1970's, Tryphonas and Nielsen" [Leander Tryphonas and N. O. Nielsen, "Pathology of Chronic Alkylmercurial Poisoning in Swine, "***American Journal of Veterinary Research***, **34**(3), pages 379-392 (1973)] "conducted a study supported by the Medical Research Council of Canada to evaluate chronic low-dose exposure to ethyl mercury and methyl mercury compounds in young swine.

The authors of that study found:

doi: 10.1588/medver.2007.04.00145

'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 given both MMD [methyl-mercury-containing compound] and EMC [ethyl-mercury-containing compound]… The results proved that the alkyl mercurial compounds MMD and EMC, if fed at low concentrations for long periods, were highly poisonous to swine.'"

"*Magos, et al.* compared the neurotoxicity and renotoxicity of alkyl mercury compounds in Parton Wistor rats. FDA acknowledges that alkyl mercury compounds, such as methyl mercury and ethyl mercury, especially when administered at high doses, are toxic; however, an extrapolation of the above data to infant exposure at far lower levels of thimerosal, and neurodevelopmental disorders, is problematic."

The **CoMeD** reviewers find that your statements here do *not* address the issues addressed by the petition, which states:

"As early as **1985**, Magos *et al*. (petition endnote 53, 'Laszlo Magos, A. W. Brown, S. Sparrow, E. Bailey, R. T. Snowden and W. R. Skipp, 'The comparative toxicology of ethyl- and methylmercury.' ***Archives of Toxicology***, **57**, pages 260-267') reported:

'Neurotoxicity and renotoxicity were compared in rats given by gastric gavage five daily doses of 8.0 mg Hg/kg methyl- or ethylmercuric chloride or 9.6 mg Hg/kg ethylmercuric chloride. Three or 10 days after the last treatment day'[,] 'rats treated with either 8.0 or 9.6 mg Hg/kg ethylmercury had higher total or organic mercury concentrations in blood and lower concentrations in kidneys and brain than methylmercury-treated rats. **In each of these tissues the inorganic mercury concentration was higher** [approximately twice as high in the brain] **after ethyl-**'[ethyl mercury]' **than after methylmercury**. Weight loss relative to the expected body weight and renal damage was higher in ethylmercury-treated rats than in rats given equimolar doses of methylmercury. These effects became more severe when the dose of ethylmercury was increased by 20%. Thus in renotoxicity the renal concentration of inorganic mercury seems to be more important than the concentration of organic or total mercury. In methylmercury-treated rats', 'damage and inorganic mercury deposits were restricted to the P2 region of the proximal tubules, while in ethylmercury-treated rats the distribution of mercury and damage was more widespread. There was little difference in the neurotoxicities of methylmercury and ethylmercury when effects on the dorsal root ganglia or coordination disorders were compared.'"

Analyzing the data, we find that the issues addressed relate to the comparative toxicities and distributions and nature of the mercury species when ethyl mercury chloride and methyl mercury chloride dosed orally into comparable groups of rats.

As a whole, this paper supports the use of the EPA "Rfd" for methyl mercury in fish as an approximate starting basis "safety" standard ceiling for Thimerosal, an ethyl mercury compound, when the required toxicological studies required to establish the "sufficiently nontoxic" (safe) level for Thimerosal in humans have *not*, as you have repeatedly admitted, been conducted.

The important findings relative to the short-term effects of these two compounds can be summarized as follows:

- For equal levels of mercury dosing, the ethylmercury-treated rats "had higher total or organic mercury concentrations in blood and lower concentrations in kidneys and brain than methylmercury-treated rats." [Indicating that, *when the mode of administration is constant*, ethylmercury chloride, *and hence Thimerosal*, clears the blood slower than methylmercury chloride.]
- "**In each of these tissues the inorganic mercury concentration was higher** [approximately twice as high in the brain] **after ethyl-**' [ethyl mercury] '**than after methylmercury**." [Indicating that ethylmercury chloride is more rapidly metabolized in the brain and kidney to "inorganic" mercury, known to have a long half-life in the brain.]
- "Weight loss relative to the expected body weight and renal damage was higher in ethylmercury-treated rats than in rats given equimolar doses of methylmercury." [Indicating that the "ethyl" compound is more toxic to the kidney and, based on weight loss, normal metabolism than the "methyl compound.]
- "There was little difference in the neurotoxicities of methylmercury and ethylmercury when effects on the dorsal root ganglia or coordination disorders were compared." [Indicating that the both compounds have comparable short-term effects on the neurological systems.]

Since the short-term neurological effects were comparable, this finding supports the findings from the long-term effects of studies that have been conducted using dosing with 0.02% levels of methylmercury hydroxide as the

doi: 10.1588/medver.2007.04.00145

organomercurial to estimate the long-term neurological effects of 0.01% Thimerosal, the maximum level in Thimerosal-preserved vaccines, since the truly long-term (over years) adverse neural effects of mercury are, of necessity, related level of "inorganic mercury" sequestered there.

In addition, this study can be used to understand that differences in inorganic mercury in the baby monkey studies of Burbacher, *et al*. (2005), which you have cited, are probably related to the innate differences in the compounds studied there rather than to the confounding differences in their routes of administration in that baby monkey study.

Finally, we find your "*…extrapolation of the above data to infant exposure at far lower levels of thimerosal, and neurodevelopmental disorders, is problematic*," concerns are *not* germane to the root issue, "safety *not* proven" in a manner that complies with *Berkovitz*,[1] **21 CFR 610.15(a)**, **42 U.S.C. 300aa-27(a)(2)**, and related applicable federal regulations and statutes, the first grounds raised by the **CoMeD** petition ("**III. Statement of Grounds A. Safety Not Proven**"), when there is clear evidence of harm from Thimerosal and proven differences in individual susceptibility.

"For example, *Tryphonas, et al.*, was concerned with consumption of parts of pig by humans derived from animals exposed to certain threshold levels of mercury that may pose health hazards."

We reiterate; the concerns of this publication are not, *per se*, germane to its findings or the information their studies provide.

"In addition, in the study by *Magos, et al.*, the cumulative dose administered to rats was 40 mg/kg which is ‹13000 times the cumulative dose that an infant less than 6 months of age would be exposed to (‹3 μg) through administration of vaccines containing trace amounts of mercury.

First, we find that the cumulative dose administered by Magos, *et al*. is not germane to the fundamental issues the **CoMeD** petition raised.

This study was offered as evidence that the neurotoxicities of Thimerosal and "methyl mercury" are similar.

"*Fagan, et al.*, analyzed samples of fresh and fixed tissues from infants with exomphalos treated by thimerosal application for mercury content."

The authors reported on 13 cases of "*exomphalos treated by thimerosal*" in which 10 of the 13 cases had died.

First, we note that the tissues were from the 10 dead infants who had received repeated (avg. 21; 9 – 48) topical applications of a "0.1-% tincture of Thimerosal (thiomersal)," where a tincture is an alcohol solution and the Thimerosal concentration was only 10X the level in a Thimerosal-preserved vaccine.

Unfortunately, the amounts of Thimerosal tincture applied were *not* recorded.

However, there was no correlation between the number of applications and the average level of mercury found in the various tissues tested.

"Results showed that thimerosal can induce blood and organ levels of organic mercury that were, as stated by the authors, in excess of the minimum toxic level in adults and fetuses. However, the authors note that 'whether the levels reported are acutely toxic or capable of producing chronic neurological damage in the newborn infant exposed perinatally… is unclear.'"

Since the infants were dead, the comment you quote is an obvious one.

However, we note that you did *not* report the authors tracked down one of the survivors when he was 10, and, *with respect to his intellectual development*, tellingly reported:

"… the school reports that he is restless, easily distracted, and not interested in schoolwork."

"We note that the authors advise against the use of mercurial antiseptics for the treatment of exomphalos or for hospital use in general. We further note that the authors' statement that equally effective and far less toxic broad spectrum antifungal and antibacterial antiseptics were available in 1977 referred to **topical** antiseptics, and not to preservatives used in vaccine products."

The **CoMeD** reviewers note that, though you were quick to address the issue of "*topical antiseptics*," you did *not* address the cogent issues raised in the petition's narrative including:

doi: 10.1588/medver.2007.04.00145

- The results showed that Thimerosal applied topically induced blood and organ levels of organic mercury that are well in excess of the minimum toxic levels in adults and fetuses.
- "Although thiomersal is an ethyl mercury compound, it has similar toxicological properties to methyl mercury and the long-term neurological sequelae produced by the ingestion of either methyl or ethyl mercury-based fungicides are indistinguishable."
- Mercury and mercury-containing compounds are highly toxic
- Alkyl mercury compounds (*e.g.*, methyl mercury and ethyl mercury [the initial mercury-containing metabolite from Thimerosal]) penetrate intact membranes.

"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"

First, the **CoMeD** reviewers note that, though the **CoMeD** petitioners asked you to:

"We also request that you review the landmark and courageous research of: Dr. Boyd Haley" petition endnote 41 ", Dr. Richard Deth" petition endnote 6(A[3]) ", Dr. Andrew Wakefield" petition endnote 61 ", Dr. Jeff Bradstreet" petition endnote 58, Dr. David Baskin" petition endnote 62 ", Dr. Mary Megson" petition endnote 63 ", Dr. Woody McGinnis" petition endnote 64 ", Dr. Amy Holmes" petition endnote 41 ", Dr. Stephanie Cave" petition endnote 65 ", and Dr. William Walsh" petition endnote 66 ",

you chose only to review the articles in petition endnotes 61, 64, and 63 here.

Second, we find that your "*Lack Evidence to Support their Theories*," addresses an issue that you have again fabricated out of "whole cloth," because, while the researchers in the articles in question put forward hypotheses (for which they did provide evidence) and *not* theories.

With these realities in mind, we will now review and address your remarks.

"FDA has also reviewed studies by *Ashwood, et al., McGinnis, and Megson*, which you cited (endnotes 61, 64, and 63). *Ashwood, et al.* (endnote 61) tested the hypothesis of a novel and characteristic enterocolitis in a subset of children with autism and gastrointestinal symptoms. The study did not examine the etiology of the enterocolitis in affected children. The authors stated that further studies are required to demonstrate potential links of these findings with disturbed cognition in autism."

We note that you agree that the researchers in Ashwood, *et al*. (petition endnote 61, "Paul Ashwood, Andrew Anthony, Alicia A. Pellicer, Franco Torrente, John A. Walker-Smith and Andrew J. Wakefield, 'Intestinal Lymphocyte Populations in Children with Regressive Autism: Evidence for Extensive Mucosal Immunopathology,' ***Journal of Clinical Immunology***, **23**(6), pages 504-517 (2003)) "*tested the hypothesis of a novel and characteristic enterocolitis in a subset of children with autism and gastrointestinal symptoms*."

While we do *not* dispute your statements, we note that this study also reported:

"The data provide further evidence of a pan-enteric mucosal immunopathology in children with regressive autism that is apparently distinct from other inflammatory bowel diseases,"

indicating that there may be a link between the causal or triggering agent for "regressive autism" and the causal or triggering agent for "pan-enteric mucosal immunopathology."

Since the symptoms of "regressive autism" are the same as those for sub-acute mercury poisoning by alkylmercurials and Thimerosal is a known immune system dysregulator, perhaps these comorbid conditions are both "caused"/"triggered" by Thimerosal exposure.

"*McGinnis* (endnote 4) suggests that toxins known to cause gut injury be considered when looking for causes of autism and that 'some specifies about autism should heighten interest in mercury.' He mentions that 'ethyl mercury as a vaccine preservative may also inflict gut injury.' No data were presented or referred to substantiate these statements. Thus, a link between ethyl mercury and gut injury as a cause for autism is speculative."

First, we note that this correspondence was speculative in nature and that the basis for the McGinnis' statements about "ethyl mercury" is both well known and well documented in other references some of which have been cited elsewhere in this petition.

Second, we note that you misquoted the author – who actually observed, based on his understanding of mercury toxicity in all its forms (as established earlier in this correspondence):

doi: 10.1588/medver.2007.04.00145

"Organic forms of mercury such as methyl mercury from fish and ethyl mercury as a vaccine preservative (thimersol" [*sic*; Thimerosal] ") may also inflict gut injury."

As to your statement, "*Thus, a link between ethyl mercury and gut injury as a cause for autism is speculative*," we suggest that you reread petition endnote 51, "Leander Tryphonas and N. O. Nielsen, 'Pathology of Chronic Alkylmercurial Poisoning in Swine, 'American Journal of Veterinary Research, 34(3), pages 379-392 (1973)," where the link between ethyl mercury and gut injury was clearly established more than 3 decades ago.

Based on the preceding, we find you either have a very short memory or, more probably, you think you can make any unsupported statement you wish to make and the reader is supposed to accept its validity simply because you have written it.

"*Megson, et al.* (endnote 63) hypothesize that autism may be a disorder linked to the disruption of the G-alpha protein and suggests that this may he reversible by treatment with natural vitamin A. The paper mentions that pertussis toxin in the DPT vaccine leads to a G-alpha protein defect causing autism in genetically at risk children. The paper also speculates that live viral measles vaccines depletes children of their Vitamin A supply. FDA finds that the conclusions reached in this paper are speculative and do not support the theory."

First, we note that the appropriate reference is simply Megson, and *not* your "*Megson, et al.*," as the petition endnote 63 clearly states:

"Mary N. Megson, 'Is autism a G-alpha protein defect reversible with natural vitamin A?,' ***Medical Hypotheses***, **54**(6), pages 979-983 (2000)."

Second we agree with you that Dr. Megson hypothesizes "*that autism may be a disorder linked to the disruption of the G-alpha protein and suggests that this may he reversible by treatment with natural vitamin A*."

Third, we also agree with you that:

"The paper mentions that pertussis toxin in the DPT vaccine leads to a G-alpha protein defect causing autism in genetically at risk children. The paper also speculates that live viral measles vaccines depletes children of their Vitamin A supply."

However, based on the preceding realities, we must reject your closing statement:

"*FDA finds that the conclusions reached in this paper are speculative and do not support the theory*."

because:

- No theory[67] was stated, *as you admit*, the paper only stated a hypothesis, "autism may be caused by inserting a G-alpha protein defect, the pertussis toxin found in the DPT vaccine, into genetically at-risk children," based on a "study of 60 autistic children."
- Since the paper states no conclusions, we are at a loss to see how you can state "*the conclusions reached in this paper are speculative*."

Finally, since you did *not* address the author's:

"Recent evidence indicates that autism is a disorder of the nervous system and the immune system, affecting multiple metabolic pathways."

we find that you have accepted the validity of this statement.

"III. PETITIONERS' LEGAL ARGUMENTS LACK MERIT"

We find that, *contrary to your assertion*, that your failure to directly address the petitioners' legal arguments in your answer implies that you found them to be valid or that you had no legal counter argument to overcome petitioners' legal arguments.

As evidence of the validity of the **CoMeD** reviewers' position, we note that you had no problem addressing the legal arguments **CoMeD** petitioners raised in the petition's sections **III. B** and **III. C**.

[67] Webster's New Universal Unabridged Dictionary, 2001, page 1967, column 3, bottom to page 1968 column 1, "the·o·ry" is scientifically defined as "a coherent group of general propositions used as principles of explanation for a class of phenomena: *Einstein's theory of relativity. …* A THEORY in technical use is a more or less verified or established explanation accounting for known facts or phenomena: *the theory of relativity*. A hypothesis is a conjecture put forth as a possible explanation of phenomena or relations, which serves as a basis of argument or experimentation to reach the truth: *This idea is only a hypothesis."*

doi: 10.1588/medver.2007.04.00145

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

Since, *as we clearly have stated*, the basis of the **CoMeD** petition includes:

- Your knowing failure to comply with **42 U.S.C. Sec. 300aa-27(a)(2)** for childhood vaccines as you are required to do by statute,
- Your admitted failure to require the manufacturers of Thimerosal-preserved biological products, including vaccines, to prove their products meet the clear "sufficiently nontoxic" requirement *minimum* set forth in **21 CFR § 610.15(a)** before you license/approve a new Thimerosal-preserved or other mercury-compound-preserved biological product or, *for Thimerosal-preserved or other mercury-compound-preserved biological products licensed before 1973*, continue to license/approve those products if and only if their manufacturer was able to provide the requisite proof , and
- Your failure, after April 1988, to restrict your administrative discretion to instances where the drug product manufacturer has complied with all of the applicable requirement minimums set forth clearly in any federal policy, law (binding regulation), or statute governing drug products as *Berkovitz*[1] clearly requires you to do,

we find that you should have either:

- Addressed these legal issues first or
- Addressed them at the same time you were addressing the scientific issues raised in the **CoMeD** petition,

and note that you did *not* address:

- The aforementioned federal law requiring the manufacturer to unequivocally prove that Thimerosal used as a preservative for a biological product is "sufficiently nontoxic" or
- The aforementioned federal statute that mandates you must take whatever actions you can (and, for biological products, those actions include the direct ability to revoke a product license) to reduce adverse reactions in vaccine approved for administration to children or
- The US Supreme Court's legal decision (Berkovitz[1]) restricting your administrative discussion.

Further, you have presented no valid scientific grounds that have refuted the fundamental propositions set forth in the **CoMeD** petition – in general, you have only made unsupported declarations or, in some cases, made statements that are provably false.

For example, you have presented no scientific proof that:

1. You or, *as directly required by **21 CFR § 610.15(a)***, the product manufacturers have proven Thimerosal-preserved biological products are "sufficiently nontoxic" to use as a preservative in said biological products, including vaccines, a perquisite, *under Berkovitz*,[1] that must be met before you can use your discretion to determine the products are "safe" and license/approve such drug products.
2. That the removal of Thimerosal from each and every licensed Thimerosal-containing childhood vaccine formulation (including vaccine formulations given to pregnant women) does *not* reduce the inoculees' risk of adverse reactions as compared to the Thimerosal-containing childhood vaccine formulation, a statutory requirement (under **42 U.S.C. Sec. 300aa-27(a)(2)**) that, *under Berkovitz*[1], you must meet before you can license/approve or continue to license/approve a Thimerosal-containing childhood vaccine.

Since you have failed to provide:

- The requisite scientific proofs to address the preceding petition issues and
- Any sound science (with, at a minimum, complete references to the articles that unequivocally prove the scientific validity of the statements you make and that these proven-valid statements refute the evidence-based statements made by the **CoMeD** petitioners) to refute the assertions made in the **CoMeD** petition,

we are compelled to find that you have failed to provide any scientific grounds to:

- Support your rhetoric or
- Overcome the evidence-based statements made in the **CoMeD** petition.

since you have provided no scientific grounds.

"For the scientific reasons discussed above in Sections I and II, none of the actions and legal remedies you seek against vaccines or other products containing thimerosal are warranted."

doi: 10.1588/medver.2007.04.00145

First, we find, *in general*, you have failed to provide any sound science, published scientifically sound toxicological studies, or references thereto, to support your statements and therefore, you have provided only your unsupported statements, which are *not* scientific reasons – but only your unsupported views.

Second, in the cases that you cited a new epidemiological study (*e. g*. your "*Fombonne, et al., 2006*") or an animal study published after the petition was submitted (*e.g.*, your "*Burbacher, et al.*") to address a contention made by the petitioners, we were able to show:

- It was fundamentally flawed and/or
- The valid data in it actually supported the petitioners' contentions.

Based on the preceding realities, we find that your responses have failed to prove that "*none of the actions and legal remedies you seek against vaccines or other products containing thimerosal are warranted*."

Furthermore, we find you *cannot* avoid the legal mandates set forth in **42 U.S.C. Sec. 300aa-27**, "Mandate for safer childhood vaccines," unless you have proven that the formulation of a vaccine that is free of all Thimerosal or other added mercurial has the same adverse risk incidence and severity as the same formulation with Thimerosal at the nominal level declared in its formula.

Since you have provide no evidence that this is the case and the **CoMeD** petition includes a peer-reviewed published report that a Thimerosal-containing formulation has a significantly higher risk of adverse reactions than the same formulation without Thimerosal (*e.g.*, Nelson and Gottshall [petition endnote 42, "E. A. Nelson and R. Y. Gottshall, 'Enhanced Toxicity for Mice of Pertussis Vaccines When Preserved with Merthiolate,' ***Applied Microbiology***, **15**(3), pages 590-593 (1967)"]), then you are legally bound to comply with this mandate.

Thus, we find that you have knowingly failed to comply with this explicit "Mandate for safer childhood vaccines" for all childhood vaccines, including vaccines given to pregnant women that are, *in effect*, also given to the *in utero* child.

In addition, while claiming since 1999 to be reducing the cumulative exposure level to Thimerosal in childhood vaccines, you:

- Added both Thimerosal-preserved and reduced-Thimerosal influenza vaccines to the national immunization for children and pregnant women in 2002 thereby increasing the maximum level of Thimerosal-derived mercury exposure for a seven-months-old routine-vaccination-schedule-inoculated child from "< 3" µg Hg when all Thimerosal-containing vaccines are reduced-Thimerosal vaccines to 53 µg after the influenza vaccines were added, without proof of safety, to the vaccination for pregnant women (thus exposing the fetus to 25 µg of mercury) and children 6-months to 23-months of age, directly adding a total dose of 37.5-µg of mercury.
- Licensed/approved a new Thimerosal-preserved influenza vaccine, FluLaval, which*, because it is licensed for adults*, can be given to pregnant women.

Thus, your actions are clearly at odds with your claim.

Based on the preceding realities, it is clear to the **CoMeD** reviewers that, *in addition to being unsupported by references and consistent with your actions*, your statements *cannot* be relied upon to be truthful.

"Therefore, we need not address your arguments about the scope of FDA's authority to take particular legal actions or to pursue particular remedies."

Given all of the preceding, your lack of legal citations supporting your statement here, and your implicit position your actions are *not* bound by the law, we must:

- Reject your unsupported assertion here, and
- Demand that you address the **CoMeD** arguments about the scope of your authority to:
  1. Ignore laws that mandate you take certain actions to safen vaccines,
  2. Knowingly license/approve drug products that do *not* meet the clear CGMP minimums (and **21 CFR § 60.15(a)** is a clear CGMP requirement *minimum*), and
  3. Based on Point **2**, collusively participate in the knowing marketing of drugs that, under **21 U.S.C. Sec. 351(a)(2)(B)**, are "deemed to be adulterated."

doi: 10.1588/medver.2007.04.00145

"Instead, we decline your request for those actions and remedies on the substantive grounds that the few vaccines and other legally marketed products that contain thimerosal are safe and that no action against those products based on their thimerosal content is appropriate."

Based on the preceding realities concerning the applicable laws and statutes, we find that, *under Berkovitz*,[1] you lack the administrative discretion to ignore said laws and statutes, and further find that your substantive grounds argument is flawed because:

You have knowingly failed to: **a)** prove or **b)** require the drug manufacturers to prove, *to the minimum "sufficiently nontoxic" standard established by* ***21 CFR 610.15(a)*** (as you have repeatedly admitted in testimony before Congress) that the marketed products that contain Thimerosal as a preservative are safe.

Therefore, the **CoMeD** reviewers again ask that you answer the **CoMeD** citizen petition in a manner that complies with all applicable policies, laws and statutes, because your answer here clearly has, *as the* ***CoMeD*** *reviewers have clearly established*, failed to do so.

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

At the end of the "Statement of Grounds" portion of your citizen petitions, you add two legal arguments as subsections B and C: "Violation Of Constitutional Right To Bodily Integrity" and "Violation of Other Civil Rights And Societal Tenants."

Before proceeding to address your response here, the **CoMeD** reviewers offer the following outline of the **CoMeD** citizen petition:

CITIZEN PETITION

I. Actions Requested (P-1 to P-6)
II. Petitioners (P-6 to P-7)
III. Statement of Grounds (P-7 to P-52)
- **A. Safety Not Proven** (P-7 to P-45)
  1. ***General Background*** (P-7 to P-8)
  2. ***Removal Of Thimerosal And Other Mercury-based Compounds From OTC Drugs*** (P-8 to P-9)
  3. ***Petitioners' General Concerns*** (P9 to P-12)
  4. ***FDA's Published Call-For-Data Notices And Announcements*** (P-13)
  5. ***Thimerosal At Multi-Dose Vaccine Or Lower Levels*** (P-13 to P-34)
     - **a.** Recent Comments of a US House Subcommittee and the US Office of Special Counsel (OSC) (P-17 to P-20)
     - **b.** "Confounded" and "Biased" Epidemiological Studies On Vaccinated Children? (P-20 to P-29)
     - **c.** Studies Establishing Linkages Between Thimerosal Exposure And Adverse Outcomes, Including "Neurodevelopmental Disorders" ("NDDs") (P-29 to P-33)
     - **d.** Inconsistencies Between The Exposure Limits For: i) Thimerosal In Drugs And ii) Methyl Mercury In Food: A Regulatory Conundrum? (P-33 to P-34)
  6. ***Ethyl Mercury, The Initial Thimerosal Metabolite*** (P-34 to P-36)
  7. ***Ionic Mercury, The Final Thimerosal Metabolite*** (P-36 to P-37)
  8. ***The Link Between Thimerosal And Neurological Disorders*** (P-37 to P-39)
  9. ***Autism Alarm*** (P-39)
  10. ***Clinical Evidence*** (P-39 to P-42)
  11. ***Significant 2004 Studies*** (P-42 to P-44)
  12. ***Summary Of "Safety Not Proven"*** (P-44 to P-45)
- **B. Violation Of Constitutional Right To Bodily Integrity** (P-45 to P-49)
- **C. Violation Of Other Civil Rights And Societal Tenants** (P-49 to P-51)
- **D. Summary** (P-51 to P-52)

IV. Environmental Impact (P-52)
V. Certification (P-53 to P-54)
Endnotes: (P-55 to P-59)

Based on the outline provided, the **CoMeD** reviewers note that petition sections "**B**" and "**C**" are integral parts of "**III. Statement of Grounds**."

With the preceding in mind, we will now address your comments concerning sections "**III. B**" and "**III. C**."

doi: 10.1588/medver.2007.04.00145

"Those two sections are not included among your Requested Actions, and you do not appear to be petitioning FDA to act on those claims. Nevertheless, FDA has the following responses to your arguments."

Since these two sections are simply additional grounds that the **CoMeD** petitioners found supported the actions they were requesting, there was no need to petition you to "*act on these claims*."

"In subsection B (page P-45 of your petition), you cite *In re Cincinnati Radiation Litigation, 874 F. Supp, 796, 810-811 (S.D. Ohio, 1995)*, *Albright v. Oliver, 510 U.S. 266 (1994)*, and *Schmerber v. California, 384 U.S. 757, 772 (1966)*, to argue that the Due Process Clause of the Fourteenth Amendment creates a substantive due process right to be free of state-sponsored invasion of a persons bodily integrity."

Factually, the **CoMeD** reviewers note that the **CoMeD** petitioners cited "*In re Cincinnati Radiation Litigation, 874 F. Supp, 796, 810-811 (S.D. Ohio, 1995), Albright v. Oliver, 510 U.S. 266 (1994), and Schmerber v. California, 384 U.S. 757, 772 (1966), to*" establish that the courts have recognized that, in your words, "*Due Process Clause of the Fourteenth Amendment creates a substantive due process right to be free of state-sponsored invasion of a persons bodily integrity*."

"You then state that 'by authorizing the manufacture, distribution, and, most importantly, the use of vaccines and other drug and biological products containing neurotoxic ingredients, including, but not limited to, Thimerosal…' the government is 'responsible for performing uncontrolled involuntary experiments on susceptible pregnant women, fetuses, newborns, children, and the rest of the public under the guise of protecting them from various diseases.' You conclude that by doing so, the government is breaching those individuals' "bodily integrity." Similarly, you argue in subsection C (page P-49 of your petition) that 'basic American civil rights and tenants (including informed consent, self determination, and personal autonomy) continue to he violated' ... 'because misled and coerced parents offer up their children for injection with mercury-laced pharmaceuticals…'"

The **CoMeD** reviewers note that, in subsection **B** (page P-46 of the **CoMeD** petition) the **CoMeD** petitioners actually stated:

> "Thus, high governmental officials, *by authorizing the manufacture, distribution, and, most importantly, the use of vaccines and other drug and biological products containing neurotoxic ingredients, including, but not limited to, Thimerosal, that have not been unequivocally proven to be safe (with at least a 10 X safety margin) to **all** who may receive said products*, have been and are, *in effect*, **responsible** for performing uncontrolled involuntary experiments on susceptible pregnant women, fetuses, newborns, children, and the rest of the public under the guise of protecting them from various diseases."

Similarly, "*in subsection C (page P-49 of your petition)*," the **CoMeD** petitioners actually asserted:

> "In addition to violating the constitutional right to bodily integrity, basic American civil rights and tenants (including informed consent, self determination, and personal autonomy) continue to be violated daily in this nation because misled and coerced parents offer up their children for injection of mercury-laced pharmaceuticals, some nominally containing 25 µg of mercury per dose with expiration dates of 2005, and, *in the case of the influenza and some other vaccines*, beyond."

"Regardless of the scope of the Due Process Cause of the Constitution and the 'basic American civil rights and tenants' on which you rely, the facts, even as you allege them, do not amount to the government violating anyone's rights."

If, *as you state*, the facts are as the petitioners "*allege them*," then, since the petitioners assert "*the knowing conduct of these responsible high governmental officials has clearly violated, and continues to clearly violate, the constitutionally protected bodily integrity rights of those susceptible individuals that have been injured*," the petitioners' assertions most certainly do amount to the government's violating "*the constitutionally protected bodily integrity rights of those susceptible individuals that have been injured*."

"For example, *In re Cincinnati Radiation Litigation* involved doctors who were alleged to have subjected indigent cancer patients to increasing levels of radiation to determine what levels that the human body can withstand, even though the doctors knew that the radiation had no therapeutic value to patients. Allegedly the doctors never informed the patients about any of those facts, but instead told them that the radiation was to treat their cancer. In contrast, here you are not denying that the vaccines and other products have prophylactic or therapeutic value to those who take them."

Addressing your assertions in reverse order, the **CoMeD** reviewers note that:

- The **CoMeD** petitioners did *not* admit "*that the vaccines and other products have prophylactic or therapeutic value to those who take them*."

doi: 10.1588/medver.2007.04.00145

- The **CoMeD** petitioners have asserted and established that, *under law*, you have represented preservative levels of Thimerosal in vaccine formulations are "safe" without having the requisite proofs of safety and in disregard for your mandate to reduce adverse effects in childhood vaccines.
- Based on studies published subsequent to the filing of this petition, we find and have noted that the in-use history for the human influenza vaccines has established that these vaccines are *not* effective.[20, 24]
- Failed to fully disclose to the recipients or their legal guardians all the risks and the true risk incidences associated with each vaccine (e.g., recent smallpox vaccine case where the claimed risk of death was 1 in 1,000,000 and, for serious harm, about 1 in 100,000, but, *as about 38,000 first providers found out*, the real rates were closer to 1 in 10,000 for deaths and 1 in 100 for severe adverse reaction),
- Inaccurately tracked the adverse reactions to vaccines by failing to provide monetary and other sanctions for the failure of a healthcare provider to report an adverse effect (*e.g.*, even the government admits that less than 10% of adverse reactions are reported to the government and entered into VAERS),
- Not assessed the long-term (beyond 6 months) risks associated with each vaccine even though there is evidence that the adverse reactions for certain may occur years or decades after inoculation (*e.g.*, the development of vaccine-related diabetes and MS in children years after hepatitis B inoculation [as the French have established] "as well as causal relationship between the hemophilus vaccine and the development of insulin dependent diabetes … 3 – 4 years after four doses of Hib"[68]),
- Understated the risks for death and serious injury from the each vaccine (*e.g.*, Varivax®)
- Inflated the effectiveness of vaccines (*e.g.*, Prevnar®),
- Failed to *fully* disclose the limitations on vaccines that do *not* cover all strains of the organism for which "protection" is claimed (*e.g.*, the vaccines for Neisseria meningitidis that provide no protection for the strain that causes about 50% of the cases of disease but the government permits the manufacturers to misrepresent those vaccines a protecting those vaccinated from contracting meningitis)

Based on the preceding facts and the preceding petition statements and reviewers' comments, the **CoMeD** reviewers are declaring:

- You have knowingly concealed the fact that the current human inactivated-influenza vaccines are *not* effective from the public and continued to recommend universal immunization for large segments of the population (*i.e.*, young children, pregnant women, the elderly).
- You have knowingly concealed and are knowingly concealing the toxicity of Thimerosal used in the formulation of vaccines and other drugs from those who are inoculated with Thimerosal-containing vaccines or, *in the case of children*, the guardians or parents of those who are inoculated with Thimerosal-containing vaccines.
- You are knowingly continuing to claim that Thimerosal-preserved and Thimerosal-containing vaccines are safe without direct toxicological proof of their safety and with a growing body of toxicological and other evidence that Thimerosal is toxic at levels approaching or exceeding 1/100,000th the 0.01% (100 ppm) level found in Thimerosal-preserved influenza vaccines.
- While claiming to be reducing Thimerosal exposure in children since 2000, you have actually been knowingly increasing some children's exposure to Thimerosal by recommending that pregnant women and children 6-months to now 59 months of age be inoculated with ineffective influenza vaccines that include Thimerosal-preserved influenza vaccines during each year's flu season.
- You have knowingly concealed the increased risks of allergy, asthma, type I and type 2 diabetes, certain leukemias, skin damage, neurological damage, immune system damage, endocrine system damage, digestive system damage, circulatory system damage, and organ damage to those inoculated with Thimerosal-containing vaccines as compared to those *not* inoculated with such vaccines.
- You have knowingly failed to accurately convey the risks, severity of risks, and the incidence of risks associated with all vaccines.
- You have knowingly overstated and/or participated in the overstating of the benefits associated with all vaccines.
- You have concealed the real reason you have recommended an at-birth inoculation of all children with the hepatitis B vaccine.
- You have concealed the long-term increased risks, to children inoculated with the hepatitis B vaccine, of their subsequently developing type I diabetes and/or multiple sclerosis.

[68] http://www.vaccines.net/newpage112.htm

doi: 10.1588/medver.2007.04.00145

Further, as a direct parallel to "*In re Cincinnati Radiation Litigation*," we have provided **Reviewer's Table 4** (**see** page S-R-116), which compares your remarks concerning the "*In re Cincinnati Radiation Litigation*" to your current recommendations for Thimerosal-preserved influenza vaccines.

Reviewer's Table 4 "*In re Cincinnati Radiation Litigation"* & US Influenza Vaccination Program

In re Cincinnati Radiation Litigation	**U.S. Recommended Thimerosal-preserved Influenza Vaccination Program**
"*... involved doctors who were alleged to have subjected indigent cancer patients to increasing levels of radiation to determine what levels that the human body can withstand*,"	Involves DHHS, including FDA and CDC who directly and indirectly, *by recommending the inoculation of their mothers when the children are fetuses,* recommended inoculating young children with *ineffective* influenza vaccines,[20, 24] including those vaccines that are Thimerosal preserved without proof of safety. [Factually, since 2002, you have *knowingly* subjected children to increasing cumulative doses of mercury from the Thimerosal-preserved influenza vaccines apparently to increase the level of harm. You knowingly did this by: 1) adding the influenza vaccines to the your recommended vaccination schedule for pregnant women and children 6-months to now up to 59-months of age and 2) allowing Thimerosal-preserved influenza to be used to inoculate these children and pregnant women with having proof of safety.]
"*… even though the doctors knew that the radiation had no therapeutic value to patients*."	You included Thimerosal-containing influenza vaccines in your immunization recommendations for young children and pregnant women even though you *knew* that these influenza vaccines were *not* effective in preventing those inoculated from getting influenza or in stopping the spread of influenza, and knew, or are responsible for knowing, that injecting Thimerosal-preserved influenza vaccines that are ineffective into pregnant women and young children mercury-poisons the children injected to varying degrees. In addition, you claimed these vaccines were safe without having proved that they were, in fact, safe.
"*Allegedly the doctors never informed the patients about any of those facts, but instead told them that the radiation was to treat their cancer."*	You never told the public the facts about the ineffectiveness of the human influenza vaccines, the risk of mercury-poisoning harm presented by Thimerosal-preserved vaccines, and the toxic properties of Thimerosal. Instead, you continued to claim these ineffective influenza vaccines were effective in preventing those inoculated from getting and/or spreading influenza and, *for the Thimerosal-containing influenza vaccines*, claimed they were safe without proof of safety and *knowingly* failed to warn those inoculated or, for children, their parents or guardians, that said Thimerosal-containing vaccines present clear clinical mercury-poisoning risks to Thimerosal-containing vaccines present clear clinical mercury-poisoning risks to themselves and/or their fetuses and children.

To the **CoMeD** reviewers, the parallels are clear.

Worse, though you have lacked scientific proof of safety since 1930 and numerous scientific articles have warned of the toxic risks of alkyl mercury compounds, including Thimerosal, including articles that found toxicity to human skin and neural tissues at the sub-ppm level that date from the 1940s, you have: a) knowingly claimed Thimerosal-preserved vaccines to be "safe" and, *since 1973*, have refused to require the manufacturers thereof to prove the Thimerosal they were using as a preservative met the clear CGMP minimum, "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," as set forth in **21 CFR § 610.15**.

In addition, since 1988, you have *knowingly* failed to act in accordance with the "Mandate for safer childhood vaccines" set forth in **42 U.S.C. 300aa-27**, which clearly required/requires you to take all possible actions to reduce the risk of adverse reactions in childhood vaccines in **42 U.S.C. 300aa-27(a)(2)**.

Thus, we find that, as agents of the government, you are even more culpable for your knowing actions than the doctors in "*In re Cincinnati Radiation Litigation*."

"Nor have you provided any evidence to claim that FDA officials have been hired to conduct 'uncontrolled involuntary experiments' on people."

Worse than being the hired agents, we find and the **CoMeD** petitioners asserted that, *as the order givers*, you, like some of the high governmental officials in the war crimes trials in Germany and Japan, are responsible.

As the **CoMeD** petitioners cogently put it, "…high governmental officials, …, have been and are, *in effect*, **responsible** for performing uncontrolled involuntary experiments on susceptible pregnant women, fetuses, newborns, children, and the rest of the public under the guise of protecting them from various diseases."

doi: 10.1588/medver.2007.04.00145

"Nor do you claim that FDA has hidden any facts from those who will use thimerosal-containing products."

First, we find that, as the **CoMeD** petitioners established, you have repeatedly *knowingly* claimed that Thimerosal-containing drugs are safe without having the required level of proof to support your claim.

Therefore, you have most certainly hidden all the facts about the risks of Thimerosal in Thimerosal-containing vaccines behind: **a)** your unsupported claims of safety and **b)** your "there is no proof" mantra from all those who are given such products.

Thus, we find that, *contrary to your protestation here*, you have, *in your words*, most certainly hidden the "*facts from those who will use thimerosal-containing products*" behind your unsupported claims of safety – an issue repeatedly raised in the **CoMeD** petition.

Therefore, we must reject your statement here because it is clearly at odds with the facts.

Second, we note that the **CoMeD** petitioners also did *not* assert the affirmative – that you had revealed the facts about Thimerosal risks to those given Thimerosal-containing vaccines or other mercury-containing drugs.

Third, we find that you have *not* required the manufacturers of vaccine and other affected drugs to provide the requisite proofs of safety as required (under **21 CFR § 610.15(a)**) so that the facts could be known and, thus, your knowing non-actions have also effectively hidden the "*facts from those who will use thimerosal-containing products*."

Based on all of the preceding facts, we find that you have knowingly concealed the facts about the risks from Thimerosal in Thimerosal-containing vaccines and, by analogy, in other mercury-product-containing drugs.

"You simply disagree with the conclusions that FDA draws from those facts."

Based on the **CoMeD** reviewers understanding of the petition and your letter purporting to respond to the **CoMeD** petition, we find that your statement here is based on an unsupported premise – namely that your conclusions are drawn from the facts presented.

"As explained above, however, FDA's conclusions are based on sound scientific principles."

Again, we find that your statement here is at odds with the facts because, as we have established, you have failed to provide or reference any body of "*sound scientific principles*" and, *in most cases*, have failed to provide any cogent citations.

Thus, we are compelled to find your conclusions are simply based on your unsupported rhetoric and *not* "*sound scientific principles*"

"Moreover, as explained extensively above, studies and other evidence support FDA's determination that vaccines and other FDA-approved products containing thimerosal are safe."

Since your extensive explanations are mostly unsupported rhetoric and the few studies and evidence you have provided have either been shown to be flawed, refuted, or shown to support the petitioners' assertions, we find your claim, "*that vaccines and other FDA-approved products containing thimerosal are safe*," is an unsupported statement that, *based on the evidence provided here and in **CoMeD**'s petition*, is at odds with:

- The body of scientific evidence presented for Thimerosal and
- In your letter and our response, the sound scientific evidence presented for phenylmercuric acetate (PMA).

"The evidence on which your petition relies either does not support your requests, or is too flawed to be considered valid scientific evidence."

First, since only scientifically sound and appropriate toxicological evidence can be used to prove the safety of highly poisonous compounds, like Thimerosal and PMA and the toxicological evidence you presented for PMA does (when properly interpreted) support the petitioner's assertion about "safety not proven" and, *since you have provided no studies that refute the scientifically sound toxicological evidence that the **CoMeD** petitioners provided*, the evidence provided does support the petition's assertion that safety has *not* been proven.

doi: 10.1588/medver.2007.04.00145

Thus, we find, *absent any evidence-based refutation of **CoMeD**'s cited scientific studies and their findings*, the evidence upon which the **CoMeD** petition is valid science that most certainly does support the requests made by the petitioners.

Second, since: **a)** the **CoMeD** petition rests upon laws and statutes and **CoMeD**'s interpretation thereof, and **b)** you have *not* addressed, much less attempted to deny, the validity of **CoMeD**'s interpretation thereof, we find that your statement here is at odds with factual reality.

"Therefore, FDA has no grounds to revoke the licenses and withdraw the approvals of thimerosal-containing products, or to take any of the other actions that you seek."

First, since you have *not* addressed the fundamental petition issue of compliance with **21 CFR § 610.15(a)** much less proven that biological drug product manufacturers are somehow *not* required to comply with this binding regulation, you have this "*grounds to revoke the licenses and withdraw the approvals of thimerosal-containing products, or to take any of the other actions that*" the **CoMeD** petitioners seek, but have obviously failed to require compliance with this clear regulation and, thereby, have acted outside the law.

You also have this legal ground because, *as you have repeatedly admitted*, the manufacturers of mercury-compound-preserved vaccines and other biological products have *not* met this requirement.

Second, since you have *not* addressed the fundamental petition issue of your mandates under **42 U.S.C. Sec. 300aa-27** much less proven that you are somehow above a statutory mandate that requires you to reduce the risk of adverse reaction in childhood vaccines (as *per* **42 U.S.C. Sec. 300aa-27(a)(2)**), you also have this "*grounds to revoke the licenses and withdraw the approvals of thimerosal-containing products, or to take any of the other actions that*" the **CoMeD** petitioners seek, but have obviously failed to comply with this clear statute and, thereby, are declaring that you are above complying with statutes that require you reduce the adverse reactions in childhood vaccines.

Third, given the 1988 unanimous Supreme Court ruling (*Berkovitz*[1]) that denies you any "administrative discretion" when there is a clear policy, law or statute that compels a given course of action, we find that you have no legal basis for:

- Your knowing failure to enforce manufacturers' compliance with **21 CFR § 610.15(a)** or
- For yourselves, to comply with **42 U.S.C. Sec. 300aa-27(a)(2)**.

Based on the preceding factual realities, you not only have the "*grounds to revoke the licenses and withdraw the approvals of thimerosal-containing products, or to take any of the other actions that you seek*" but also are compelled by the highest law in the law in the land, the US Supreme Court in *Berkovitz*,[1] to use those ground to take the actions the **CoMeD** petitioners have properly petitioned you to take.

"Consequently, even if constitutional or other 'civil rights' were considered to exist in this context, declining to take any action against those products does not violate anyone's constitutional or other rights."

For the cogent reasons asserted throughout this review and in the **CoMeD** petition, we must reject your unsupported statement here because, *as the **CoMeD** petitioners and we have shown*, it flies in the face of the clear protections afforded all citizens under the Fourteenth Amendment of the Constitution of the United States of America as interpreted by the courts and your actions to conceal the risks from Thimerosal behind unsubstantiated claims of safety that are, in part, unsubstantiated because you have refused to act to:

a. find or

b. as **21 CFR § 610.15(a)** clearly compels the manufacturers of Thimerosal-containing and/or other mercury-compound containing vaccines and other drug products to do, prove

what the real risks of these mercury-containing compounds when used as a preservative are to the most susceptible children.

"IV. AGENCY CONCLUSIONS

For the reasons discussed above, the studies and other documents on which you rely do not support your argument that FDA should take action against biologics and other drugs that contain thimerosal."

We must reject your statement here based on:

- The evidence-supported reasons presented in this review and in the petition and

doi: 10.1588/medver.2007.04.00145

- Your failure to present any cogent evidence-supported rationale to refute the evidence provided, the claims made by the petitioners, or the laws, statutes, and court decisions upon which the **CoMeD** petition is based.

"Only a small number of licensed and approved products still contain thimerosal, and the available evidence supports FDA's conclusion that all currently licensed vaccines and other pharmaceutical drug products containing thimerosal are safe."

We must reject your statement here because:

1. Compliance with the laws and statutes compelling certain actions or the meeting of certain standards dos *not* depend on the fact that "*a small number of licensed and approved products still contain thimerosal*," and
2. Contrary to your unsupported statements and opinions, the body of scientific, legal, and historical evidence clearly supports the petitioners' "**Safety Not Proven**" grounds,
3. Since you have not denied that **21 CFR 610.15(a)** is a legally binding requirement on the manufacturers of all preserved biological products, including vaccines preserved with Thimerosal or that the manufacturers of said products have *not* complied with **21 CFR 610.15(a)**, all such drugs are, as the **CoMeD** petitioners have asserted, adulterated under **21 U.S.C. 351(a)(2)(B)** and, therefore, illegal to be on the market,
4. Under *Berkovitz*,[1] you have lack the administrative discretion to allow these violative (adulterated) products to remain on the market especially since you assert that only "*a small number of licensed and approved products still contain thimerosal*," and
5. As the **CoMeD** reviewers have reported, recent published studies[20, 24] have proven that one of these Thimerosal-containing vaccines, the influenza vaccine is *not* effective.

"For these reasons, we deny your petition in its entirety.

Sincerely,

"Jeffery Shuren's signature"

Jeffrey Shuren, M.D., J.D.
Assistant Commissioner for Policy"

Since you letter has failed to provide any cogent evidence-based rationale that overcomes the issues raised in the petition and you have failed to mention, much less address the legal issues raised, the **CoMeD** reviewers are compelled to reject your decision because it is lacking in substance and at odds with the laws governing your conduct.

Respectfully,

["digital" signature of Dr. King]

Paul G. King, PhD,
Science Advisor
CoMeD

"Enclosure: Table — Thimerosal Content of Vaccines Routinely Recommended for Children 6 Years of Age and Younger."

doi: 10.1588/medver.2007.04.00145

Table 1. Thimerosal content of vaccines routinely recommended for children 6 years of age and younger *(updated 7/18/2005[1])*
[1]Since this update, a biologics license application was approved for Rotavirus Vaccine, Tradename-RotaTeq (Merck), that is thimerosal free and never contained thimerosal.

Vaccine	Tradename (Manufacturer)*	Thimerosal Status Concentration**(Mercury)	Approval Date for Thimerosal Free or Thimerosal / Preservative Free (Trace Thimerosal)*** Formulation
DTaP	Infanrix (GSK)	Free	Never contained more than a trace of thimerosal, approval date for thimerosal-free formulation 9/29/00
	Daptacel (AP)	Free	Never contained Thimerosal
	Tripedia (AP)	Trace (≤0.3 µg Hg/0.5mL dose)	03/07/01
DTaP-HepB-IPV	Pediarix (GSK)	Trace (<0.0125 µg Hg/0.5mL dose)	Never contained more than a Trace of Thimerosal
Pneumococcal conjugate	Prevnar (WL)	Free	Never contained Thimerosal
Inactivated Poliovirus	IPOL (AP)	Free	Never contained Thimerosal
Varicella (chicken pox)	Varivax (M)	Free	Never contained Thimerosal
Mumps, measles, and rubella	M-M-R-II (M)	Free	Never contained Thimerosal
Hepatitis B	Recombivax HB (M)	Free	08/27/99
	Engerix B (GSK)	Trace (<0.5 µg Hg/0.5mL dose)	03/28/00
Haemophilus influenzae type b conjugate (Hib)	ActHIB (AP)/OmniHIB (GSK)	Free	Never contained Thimerosal
	PedvaxHIB (M)	Free	08/99
	HibTITER, single dose (WL)[1]	Free	Never contained Thimerosal
Hib/Hepatitis B comb.	Comvax (M)	Free	Never contained Thimerosal
Influenza	Fluzone (AP)	0.01% (12.5 µg/0.25 mL dose, 25 µg/0.5 mL dose)[2]	
	Fluzone (AP)[3] (no thimerosal)	Free	12/23/2004
	Fluvirin (Chiron/Evans)	0.01% (25 µg/0.5 mL dose)	
	Fluvirin (Chiron/Evans) (Preservative Free)	Trace (<1ug Hg/0.5mL dose)	09/28/01
Influenza, live	FluMist[4] (MedImmune)	Free	Never contained Thimerosal

Manufacturer abbreviations:
GSK = GlaxoSmithKline; WL = Wyeth Lederle; AP = Aventis Pasteur; M = Merck.
** Thimerosal is approximately 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of thimerosal contains 50 µg of Hg per 1 mL dose or 25 µg of Hg per 0.5 mL dose.
*** The term "trace" has been taken in this context to mean 1 microgram of mercury per dose or less.
1 HibTiITER was also manufactured in thimerosal-preservative containing multidose vials but these were no longer available after 2002.
2 Children 6 months old to less than 3 years of age receive a half-dose of vaccine, i.e., 0.25 mL; children 3 years of age and older receive 0.5 mL.
3 A trace thimerosal containing formulation of Fluzone was approved on 9/14/02 and has been replaced with the formulation without thimerosal.
4 FluMist is not indicated for children less than 5 years of age."

doi: 10.1588/medver.2007.04.00145