

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:

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

[Note: Text continued from page P-296.]

“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, EPA’s “best guess” as to a safe *maximum* daily intake exposure level for adults.

“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.”

Petitioners respectfully disagree with the letter’s 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/or disrupt normal function) and that Thimerosal also directly damages (dysregulates) the human immune system (and, in some cases induces detrimental autoimmune responses).

Though this letter later alleges that Thimerosal is *not* an adjuvant,²⁹⁵ Eli Lilly officials clearly hold a somewhat different view.²⁹⁶

²⁹⁵ Adjuvant is a substance mixed with an immunogen in order to elicit a more marked immune response.

Speaking of Thimerosal at the 1999 "Lister Hill" workshop on "**Thimerosal in Vaccines**," Dr. Jeffrey Englhardt, an Eli Lilly Senior Research Scientist, 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."²⁹⁷

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 to the petitioners 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 immune response elicited from the same formulation without the Thimerosal.

In addition, as Dr. Englhardt reported, Thimerosal can trigger a "systemic hypersensitivity reaction" in humans though not in rabbits or guinea pigs.

Further, petitioners cite the Pittman Moore experience (see 200P-0349/CP1's 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

²⁹⁶ 2004P-0349/CP1 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.

²⁹⁷ *loc. cit.*, Day1, pages 95-96.

on humans and find that it gives a more marked local reaction than does phenol and tricresol.’”²⁹⁸

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

In addition, we note that, *in addition to being highly toxic*, Thimerosal is a human teratogen, carcinogen, mutagen, and immune system dysregulator capable of inducing strong autoimmune havoc at sub-ppm levels. [See: MSDS documents from Eli Lilly & Co. (1999) and Sigma Chemicals Co. (2002) for more detailed general toxicity information on Thimerosal.]

However, petitioners do agree with the FDA’s stated assessment that “*the data are insufficient ... to set limits based on toxicity*” and observe that this statement is a clear admission that the FDA is fully aware of the reality that the vaccine manufacturers have not submitted, and may have not conducted, the toxicity studies required to prove that, *in each of their formulations*, Thimerosal is “sufficiently nontoxic ...” as said manufacturers have been required by law to do since 1973, if not earlier.

“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

²⁹⁸ Stetler HC, Garbe PL, Dwyer DM, Richard R, Facklam RR, Orenstein WA, West GR, Dudley KJ, Bloch AB. Outbreaks of group A streptococcal abscesses following diphtheria tetanus toxoid-pertussis vaccination. *Pediatrics* 1985; 75(2): 299-303.

(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 weighs 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 1/3rd the adult dose and roughly 1/28th the child's dose.

Based on the concentration and species differences (rabbits are less susceptible to immune system poisoning [as, for example, Eli Lilly's Dr. Jeffrey Englhardt stated in the 1999 Lister Hill workshop]), petitioners 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 µg/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."

Petitioners accept the FDA's estimation of the maximum dose of Thimerosal as 25 mg/day or 5 µg/kg/day in a 50-kg person.

However, the petitioners again dispute the use of the NOEL for rats as we find that,

based on current science,²⁹⁹ a better “guideline” value is one-tenth the EPA’s estimated RfD for “methylmercury,” based on human consumption of fish containing protein bound methylmercury (0.1 µg/kg/day), or 0.01 µg mercury/kg/day, because:

- That EPA limit 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, or more than twice,³⁰⁰ the toxicity of “methyl mercury.”

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

In addition, this study failed to report the percentages of the mercury excreted from the amounts of Thimerosal injected.

Furthermore, *in studies dating from the 1940s*, Engley³⁰¹ reported that Merthiolate (Thimerosal) and phenylmercury borate had similar toxicities to each other in bacterial studies and studies on human skin and notochord tissue samples.

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- ²⁹⁹ a. Gosselin NH, Brunet RC, Carrier GT, LeBouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data. *J Exposure Anal Environ Epidemiol* 2006; **16**(1): 19-29.
- b. Canuel R, Boucher de Grosbois S, Atikessé L, Marc Lucotte M, Arp P, Ritchie C, Mergler D, Chan HM, Amyot M, Anderson R. New Evidence on Variations of Human Body Burden of Methylmercury from Fish Consumption. *Environmental Health Perspectives* 2006 Feb; **114**(2): 302-306.
- c. Gilbert SG, Grant-Webster KS. Neurobehavioral effects of developmental methylmercury exposure. *Environmental Health Perspectives* 1995; **103**(Suppl 6): 135-142.
- d. Rice DC, Evangelista de Duffard AM, Duffard R, et al. Lessons for neurotoxicology from selected model compounds: SGOMSEC joint report. *Environmental Health Perspectives* 1996; **104**(Suppl 2): 205-215.
- e. Grandjean P, Budtz-Jorgensen E. Total imprecision of exposure biomarkers: implications for calculating exposure limits. *Am J Ind Med*. 2007 May 9; [Epub ahead of print]
- ³⁰⁰ Tryphonas L, Nielsen NO. Pathology of chronic alkylmercurial poisoning in swine, “*American Journal of Veterinary Research*. 1973; **34**(3): 379-392.
- ³⁰¹ a. Engley FB. Evaluation of mercurial compounds as antiseptics. *Ann. N. Y. Acad. Sci.* 1950; **53**: 197-206.

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 guideline level of 0.1 µg mercury/kg/day and 500 times the putative safety level for “susceptible” individuals, if the EPA guideline were to be updated with the current understanding of its overestimation of the safe level in humans. **[Note:** Adverse reactions to Thimerosal-preserved contact lens products are known to occur in adults.]

Moreover, if the ophthalmic solutions were given to a child weighing 5 kg, petitioners note that the dose would be 500 times the EPA guideline of 0.1 µg of mercury /kg/day.

In addition, petitioners note that, based on the FDA’s 1999 list (see pages P-186 – P-187 of this citizen petition), ophthalmic products can contain up to 0.01% Thimerosal and, *using the same calculations*, the exposure risks would obviously be 10 times higher than these in the least-level ophthalmic solutions that the FDA chose to use as their example.

Based on the preceding considerations, the petitioners find that, *contrary to the letter’s view*, the use of Thimerosal in ophthalmic products *clearly poses “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 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.”

b.Engley FB. Mercurials as Disinfectants: Evaluation of Mercurial Antimicrobial Action and Comparative Toxicity for Skin Tissue Cells. Chicago, IL: 42nd Mid-Year Meeting of the Chemical Specialties Manufacturer's Association (1956).

In general, petitioners again 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, for the reasons cited in the previous discussion on ophthalmic products, petitioners again assert that the EPA’s human-derived value (0.1 µg/kg/day), and not the rat value, should be used as an upper limit for safety basis for mercury in Thimerosal-preserved nasal sprays and find that the maximum dose the letter calculates again exceeds the EPA guideline 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 guideline level, this dose would probably only be safe for person who weighed more than 250-kg (551 lb).]

Finally, the petitioners note that PMA is also used and, for humans, the EPA has established a daily guideline dose of 0.08 µg mercury/kg/day leading to level that exceed this EPA “ADI” guideline by a factor of about “6” for a 50-kg person and by a factor of about “60” for a 5-kg child. **[Note:** Most nasal sprays in the FDA’s 1999 list (see page P-185 of this petition) use phenyl mercuric acetate (PMA) and not Thimerosal.]

“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 study³⁰² established that the intake of mercury from fish is much lower than the levels estimated by the EPA

³⁰² Gosselin NH, Burnet RC, Carrier G, Bouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data. *J Expo Anal Environ Epidemiol.* 2006 Jan; 16(1): 19-29. [E-pub 29 June 2005 (www.nature.com/jea): 1-11. Erratum in: *J Expo Sci Environ Epidemiol.* 2006 Jul; 16(4): 386.]

and, *contrary to the EPA's assumption that the levels of mercury in hair were proportional to exposure*, more recent studies were able to show that, *in some of the children tested*, there was no correlation between the two,^{303,304} but

- The EPA's human-based standard based on the consumption of methylmercury in fish is still a better estimate than the putative NOEL for Thimerosal in studies of rats,

petitioners 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 "guideline" 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 "guideline" for Thimerosal is probably 0.01 µg/kg/day or lower.

Finally, because: **a)** a 0.001-ppm level of Thimerosal has been proven to be toxic to growing human neuron system by Parran et al. and **b)** Thimerosal has been shown to be a bioaccumulate in the brains of developing monkeys as "inorganic mercury" by Burbacher et al., petitioners:

- 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, *based on the current understanding of the toxicity of Thimerosal and the current*

³⁰³ Redwood L, Bernard S, Brown D. Predicted Mercury Concentrations in Hair From Infant Immunizations: Cause for Concern. *NeuroToxicology* 2001; **22**: 691-697.

³⁰⁴ Holmes AS, Blaxill MF, Haley BE. Reduced Levels of Mercury in First Baby Haircuts of Autistic Children. *Int J Toxicol* 2003; **22**: 277-285.

EPA RfD 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 for “susceptible” humans.

Further, the petitioners note that letter’s “*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*” is, at best, a *non sequitor* because Thimerosal is a systemic poison that: **a)** is readily absorbed, **b)** crosses the blood-brain barrier, and **c)** breaks down into “inorganic mercury” in the brain where it becomes a long-term toxin and immune-system dysregulator.

Based on all of the preceding realities, it is clear to the petitioners that: **a)** the level of Thimerosal in “ear drop” products is more than sufficient to mercury poison a child and **b)** there are documented cases of such mercury poisonings.³⁰⁵

“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 [sic; 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).”

The petitioners first note that the FDA has again failed to state the fundamental position in 2004P-0349/CP1, which, *when reduced to its basics*, asserts:

The Secretary of HHS, and CDC, FDA and NIH officials have knowingly failed to:

- Comply with federal statutes requiring that these officials to do all that they can to reduce adverse reactions in childhood vaccines that contain any level of Thimerosal or other mercury-based compounds, as required by **42**

³⁰⁵ Rohyans J, Walson PD, Wood GA, et al. Mercury toxicity following merthiolate ear irrigations. *J Pediatr* 1984; **104**: 311-313.

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 including 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, **under 21 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 by the U.S. Supreme Court in 1988 in *Berkovitz v. U.S.* on the administrative discretion of federal officials.

Nowhere in this letter do the petitioners find that the writer of the letter has:

- Explicitly addressed any of the aforesaid issues in factual manner or
- Denied that these issues are applicable to the failure of the Secretary of HHS and responsible CDC, FDA and NIH officials, subordinates that work under the Secretary’s direction, to:
 - Comply with the laws and statutes governing their conduct,
 - 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, and/or

- Act to: **a)** remove obviously adulterated drugs (under **21 U.S.C. § 351(a)(2)(B)**, adulterated by the failure of the drug manufacturers to meet the CGMP *minimum* for proof of safety to the standard “sufficiently nontoxic ...” set forth in **21 C.F.R. § 610.15(a)** for drugs preserved with Thimerosal, PMA, or another mercury-containing compound) from the market and **b)** pursue the mandated legal action against the manufacturers these adulterated drug products.

The petitioners further note that the Secretary of HHS and the accountable FDA and NIH officials, *indirectly*, and the manufacturers of preserved drug products, *directly*, have the burden of proving drug safety to the CGMP minimum of “sufficiently nontoxic ...” – *a burden that FDA officials have repeatedly admitted and/or testified neither group has met.*

Moreover, because the CGMP minimum is “sufficiently nontoxic ...,” the requisite proofs must be based on scientifically sound and appropriate toxicity studies, using the labeled mode of administration for each such preserved drug product, in primates or in other animal models proven to mimic human response and human sensitivity to mercury poisoning – not in oral studies using a generic rat strain.

Furthermore, the federal courts have repeatedly ruled that the duty to prove safety is a absolute non-dischargeable duty that the drug manufactures have – and, therefore, the responsibility to prove safety cannot be transferred to the general public or to any group of petitioners, as this letter repeatedly attempts to do whenever it speaks to the **lack of evidence of harm** instead of, *what is required*, **proof of safety.**

Since: **a)** the FDA and the CDC have approved using these Thimerosal-preserved drugs in pregnant women and **b)** 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 control sets who are given a “no Thimerosal” counterpart.

As FDA’s repeated use of the phrase “lack of evidence of harm” reveals, *despite having failed to conduct these studies or to require the manufacturers to conduct and submit the requisite toxicity studies*, the Secretary of HHS and responsible FDA officials: **a)** have apparently *knowingly* violated the law, *as established by Berkovitz v. U.S.*, 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 and **b)** have acted, *and are acting*, in direct contravention of the 1988 statutory mandate to reduce adverse reactions in “childhood” vaccines as set forth in **42 U.S.C. Sec. 300aa-27(a)(2)**. [Note: Had the Secretary of HHS and these FDA officials heeded the 1988 mandate set forth in **42 U.S.C. 300aa-27(a)(2)**, they would not have approved the Thimerosal-preserved formulations of the currently licensed Hib, hepatitis B, DTaP, and influenza vaccines (*approved in the late 1980s, early 1990s, and subsequently*).]

Based on the FDA’s on-going 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 C.F.R. Part 211**, *in general*, and **21 C.F.R. § 211.1**, *in specific*) for finished pharmaceutical products.

Further, *contrary to your views*, we find that all that the 2004P-0349/CP1 petition 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 (ppm) “when comparable levels of other ionic heavy metals and ionic aluminum have been shown to cause no observable” harm – where the approximately 0.02 ppm mercury level is 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}

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

Petitioners can only agree that 2004P-0349/CP1 “cited work done by Leong, et al. (2001), in support of” 2004P-0349/CP1’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 ($1 \times 10^{-7}M$) 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 the petitioners are glad this letter acknowledged these data, we note that the FDA has misstated the paper's findings because the authors found that mercury did more than "*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 petitioners in 2004P-0349/CP1 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 petitioners 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 petitioners find the remarks here even more curious and non-relevant since, *as the quote in the next statement in this letter confirms*, 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 petitioners note that the letter has again misrepresented the text from the 2004P-0349/CP1 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).”

Second, the petitioners observe that the FDA has quoted a portion of a note to an issue without including its context – an action that further distorts the remark.

Properly, *in context*, the text states (with underlining added to highlight the portion of the “**Note**” you chose to quote) [see the 2004P-0349/CP1 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 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 ...]”**

Otherwise, the petitioners do not disagree with the FDA’s 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 petitioners note that the FDA’s letter has again misquoted the petition here by leaving out the bolding and the underlining emphases, as 2004P-0349/CP1

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 2004P-0349/CP1 petition’s page P-11.]

Thus, the issue raised in 2004P-0349/CP1 was that neurotoxicity is 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 the FDA letter has 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 petitioners agree with the FDA’s representation here.

However, the petitioners object to the letter’s failure to state that these effects include cell death and non-reversible 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 data ...,” the FDA is implicitly acknowledging that they are valid data.

However, the issues the 2004P-0349/CP1 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 either 2004P-0349/CP1 or, for

that matter, this citizen petition.

Thus, petitioners find that the FDA's 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 a fundamental issue underlying this citizen petition as it was in the 2004P-0349/CP1 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, the petitioners suggest that the FDA and any subsequent reviewer of the petitioners' assessment of this petition simply ignore FDA's remarks here because they are not relevant to the key mercury-poisoning issues raised in this petition and in 2004P-0349/CP1.

"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)."

Since the FDA does not dispute that the cited studies address the toxicity of mercury, petitioners again suggest that this non-relevant 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."

The petitioners 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, petitioners simply reject the FDA’s 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, petitioners find that the letter has failed to provide any proof of safety for the drug products in question or a scientific basis for dismissing any, or all, of the studies referenced.

Second, the FDA’s response oddly addresses the tangential issue of Thimerosal’s causing autism, *an issue recognized by Congress in 2003,*³⁰⁶ but fails to address one of the crucial 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: *“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.

³⁰⁶ **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].

For example, in acute toxicity studies, the levels administered are, *for obvious reasons*, overdoses – else how would an 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, petitioners agree that the *“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 the 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,”* the FDA has failed to establish any linkage between the reported behavior of Tylenol, typically taken at doses of 200 mg to 800 mg or higher, and Thimerosal and related mercury-based preservatives with per-dose mercury levels of 0.05 mg to < 0.005 mg.

Further, in cases where a compound is acutely toxic and its metabolic products are bioaccumulative, 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 some cases*, be reversed, blocked or mitigated 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), petitioners find that the FDA should be focusing what the FDA is 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 C.F.R. § 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 petitioners must reject the FDA’s conclusion because the Agency:

- a. Has failed to prove: or
- b. *As required by law*, have the manufacturers prove:

the level of Thimerosal in Thimerosal-preserved vaccines or other biological drug products meet the safety *minimum* set forth in **21 C.F.R. § 610.15(a)** for preservatives (or, *implicitly*, the manufacturers of other Thimerosal-preserved drugs); or, *simply*, the level of Thimerosal or other mercury-based compound used as a preservative in any drug is “sufficiently nontoxic”

The petitioners find that the FDA is attempting to avoid the legal reality that the burden of proving safety to the established regulatory minimum standard is the non-dischargeable absolute duty that the vaccine makers and other drug manufacturers are required to meet and that, under *Berkovitz v. U.S.*, you have no administrative discretion to approve/license (or continue to approve of license) any drug product that fails to meet a clear policy, law or statute, including but not limited to **21 C.F.R. § 610.15(a)** explicitly (for preservatives in biological drug products) and **21 U.S.C. § 351(a)(2)(B)** implicitly (for all drugs), that contain a requirement minimum that must be met before approval or licensing can be granted or legally continued.

In addition, petitioners find that the FDA has *knowingly* failed, since December 22, 1987, to meet the statutory mandate set forth in **42 U.S.C. § 300aa-27(a)(2)** to reduce the adverse reactions in all childhood vaccines.

Finally, petitioners note that, *since the Congress of the United States of America has determined that there is a probable connection between Thimerosal in vaccines and autism,*³⁰⁷ you should take up this issue with Congress.

This is the case because Congress, and not the petitioners, determined that this link existed in May of 2003, *more than a year before the 2004P-0349/CP1 petition was submitted to the FDA for consideration in August 2004*, as those petitioners clearly stated in their petition (**see** pages P-17 and P-18 of 2004P-0349/CP1):

“ 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 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.”

Finally, the petitioners 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*

³⁰⁷ 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.

product's benefits to users will outweigh its risks," has been limited by the U.S. Supreme Court in a unanimous 1988 decision, *Berkovitz v. U.S.*, which clearly requires that a manufacturer must meet all applicable legally policies, laws and statutes before the FDA can legally exercise the Agency's administrative discretion to license or 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, petitioners note the FDA has:

- Taken these studies out of the context in which they were presented, and,
- By so doing, distorted the reasons they were cited and their importance to 2004P-0349/CP1.

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

Factually, the cited articles are 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, as *2004P-0349/CP1 and the current citizen petition have established*, have a significant mercury-poisoning component.

In that regard, petitioners note that these studies were cited 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*, has 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*, that administering a mercury compound causes mercury poisoning – a straightforward proposition).

Thus, the cited animal model studies show mercury toxicity following administration of Thimerosal to animal model systems that, *to varying degrees*, mimic potential human exposures to Thimerosal from pharmaceutical products.

Once again, the petitioners find the FDA attempting to dismiss these studies without providing a scientific rationale to justify the Agency's rejection of these studies with respect to their showing mercury toxicity in animals following Thimerosal administration – the same issue the petitioners are addressing in this part of the current 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 these comments, the petitioners must note that, with respect to this study, the 2004P-0349/CP1 petition stated (with underlining added to highlight the important issues addressed):

“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 antifibrillar 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 2004P-0349/CP1 petition pages P-43-44.]

Though this 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,*" the FDA 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." [See 2004P-0349/CP1's endnote 60.]

With respect to the FDA's "*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,*" the petitioners find that, the researchers' apparent assumption that humans respond with the same insensitivity/sensitivity to mercury as mice respond is not supported by any evidence that these researchers and/or the FDA presented.

Furthermore, *returning to the PMA discussion*, the FDA should 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 antifibrillar antibodies” (2.5 mg thimerosal/l [2.5 ppm Thimerosal]) and “the absorbed dose” (“147 microg Hg/kg bw”) by 100 and, using that correction factor, estimated the human “absorbed dose” that would not trigger human autoimmune response as 1.47 µg Thimerosal/kg.

Based on this human-appropriate “absorbed dose” estimate 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. **[Note:** In actuality, there are documented cases where children receiving a Thimerosal-preserved vaccine injection have developed a systemic “autoimmune” reaction.]

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

Since, as the Agency admits, the statement quoted, “***there exists no significant risk for de novo induction of systemic autoimmunity in humans due to thimerosal in vaccines***”:

- Is based on an unsubstantiated assumption that “using the dose-response data in mice” is appropriate for humans, and
- Conflicts 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,”

this paper actually supports the reality that Thimerosal does mercury poison, and has actually mercury-poisoned, human infants and children to the point that the affected persons exhibit “acrodynia” — a known form of clinical mercury poisoning.³⁰⁸

Thus, petitioners find that the FDA’s 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.”

Here, the petitioners agree with the FDA 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., petitioners find that the FDA’s statement here subtly mischaracterizes the researchers work by substituting the word “assume” for the word actually used, “hypothesize.”

Second, as the researchers stated in the paper’s abstract (with underlining added to highlight the issue at hand):

³⁰⁸ **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*”

“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, ...” (2004P-0349/CP1 petition’s endnote 59),

which clearly indicates that they made no assumptions, but were rather trying, as scientists do, to test a *working hypothesis*.³⁰⁹

As these researchers clearly stated, their *working hypothesis* was:

“autoimmune propensity influences outcomes in mice following thimerosal challenges.”

Thus, what these researchers 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 the same “autoimmune propensity” as controls.

Thus, the FDA’s, “*assume that autism is caused by an autoimmune reaction,*” is a *knowing* misrepresentation of the facts relating to this study.

As the title of their paper, “Neurotoxic effects of postnatal thimerosal ...,” clearly states, they were studying “the neurotoxic hazard posed by mercurials” to the “developing brain,” and not FDA’s 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.*”

³⁰⁹ Webster’s New Universal Unabridged Dictionary, 2001, page 945, column 1, “**hypothesis**” 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.”

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,*” the FDA’s statement here is *apparently* a knowing attempt on the Agency’s part to further mislead any reader of this FDA letter and, *as such*, is scientifically, and may legally be, in the wrong.

Based on the preceding facts, petitioners find that FDA’s statement adds nothing to the facts that this research paper established.

Factually, petitioners confirm the 2004P-0349/CP1 petition reported these important findings and that 2004P-0349/CP1 reflected the researchers’ work as follows (with underlining added to highlight the underlying issues [see 2004P-0349/CP1 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, which are not similarly 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 the work of Hornig *et al.* is that they were able to duplicate: **a)** the symptoms and **b)** altered brain structures that have been found and reported when developing children are mercury poisoned.

These researchers accomplished the aforementioned outcomes by dosing neonatal SJL/J mice with Thimerosal under conditions mimicking those experienced by a developing human child inoculated in a manner paralleling a recommended U.S. childhood immunization schedule.

Thus, their results proved 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-preserved-vaccines-toxicity-assessment protocol.

Therefore, their work provided direct evidence (proof) 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, Hornig et al.:

- Established Thimerosal-preserved vaccines represent a mercury-poisoning risk to some neonates but not to other neonates, 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*,” the FDA’s statement here should be ignored because, *though it does express the Agency’s views*, this statement fails to address the findings in the Hornig et al. study.

Moreover, this statement does not challenge the validity of the Thimerosal-derived mercury neurotoxicity findings (behavioral and structural) reported by Hornig et al. for developing mice from a strain of mice that were susceptible to mercury poisoning.

“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 the FDA’s 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 C.F.R. § 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 petitioners are, *at best*, bemused by your comment here.

Petitioners therefore again ask the FDA to enforce this clear CGMP minimum requirement for toxicological proof of safety to the CGMP minimum standard “sufficiently nontoxic ...” (as set forth in **21 C.F.R. Sec. 610.15(a)** for all preserved biological products, including biological products containing Thimerosal or other mercury-based compounds as a preservative) for all preserved drug products.

This should be the Agency’s finding because, just as the definition of “safety” set forth in **21 C. F. R. Sec. 600.3(p)** implicitly applies to all drugs, this “sufficiently nontoxic ...” CGMP minimum implicitly applies, given **21 CFR Part 210** and **21 U.S.C. 351(a)(2)(B)**, to all preserved drugs.

Moreover, the FDA’s “*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 explicitly

proclaims that animal models are valid for evaluating the toxicity of Thimerosal in vaccines.

However, petitioners observe with dismay that, *when studies presented in the 2004P-0349 petition clearly showed toxicity from Thimerosal and ethylmercury in animals*, the FDA has decided not only to give them no weight but also to address issues of the Agency's own creation instead of accepting and addressing the clear evidence of Thimerosal toxicity presented in 2004P-0349/CP1.

Hopefully, in their review of this citizen petition, the Secretary of HHS and the responsible FDA officials will not again allow this subjective treatment of the evidence submitted to recur and will, *instead*, make consistent observations derived from scientifically sound and appropriate evaluations of the proofs of both toxicity and harm in the cited supporting documents.

Further, because the petitioners 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 2004P-0349/CP1 was filed*, in this evaluation of the FDA's position statements.

These are studies in which the researchers 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 are being given:

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 Th1-dependent serum immunoglobulins. Antinucleolar antibodies (ANoA) targeting the 34-kDa nucleolar protein fibrillar, 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 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."

By citing these additional papers, *published in journals readily available to the FDA*, the petitioners trust that the Agency will now *clearly* see that the key issue this citizen petition is addressing here, *like the issue that 2004P-0349/CP1 addressed previously*, is the issue of Thimerosal toxicity in animal models at low levels of exposure – an issue that directly bears on the issue of Thimerosal safety in vaccines and other drugs.

Hopefully, *after evaluating this citizen petition*, the FDA will refrain from addressing issues outside of those raised by the current petitioners.

“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 petitioners find your statement here problematic because it indicates, for vaccines, the Secretary of HHS and CDC and FDA officials are failing to properly discharge their duty (statutory mandate), under **42 U.S.C. Sec. 262(a)(2)(C)**,³¹⁰ to ensure that vaccines are safe for the fetus before authorizing any vaccine to be administered to a healthy pregnant woman who is disease free and has little, or no, risk of contracting a disease that truly threatens the life of the fetus.

Based on the Agency’s 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,”* the Secretary and the Secretary’s responsible subordinates in the CDC, FDA and NIH are admitting that you:

- *Knowingly* failed to require the requisite proof of safety for the fetus before you authorized the Thimerosal-preserved influenza vaccines to be routinely administered to pregnant women, when feasible, in 2002 and
- Have *knowingly* continued to disregard your statutory mandates and recommend pregnant women be vaccinated with Thimerosal-preserved vaccines without the required proof of safety to the fetus until the present time, July of 2007.

Hopefully, the pregnant American women and American women of childbearing age and their husbands, parents, and other relatives, will be appropriately angered by your lack of concern for the safety of their unborn children, when they discover your knowing failure to require Thimerosal-preserved vaccines and other mercury-

³¹⁰ **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 -

(l) the biological product that is the subject of the application is safe, pure, and potent; ...”

containing drug products given to pregnant women to be proven safe for the children developing in the womb (to the standard “sufficiently nontoxic ...”) before recommending their routine use, as required by statute.

Also, the petitioners find it outrageous that, despite the admission that animal models should be used “*to evaluate the potential of the vaccine to harm the developing fetus, you recommended Thimerosal-preserved Rho(D) biological products and Thimerosal-preserved inactivated-human-influenza vaccines, supposedly required to be the “safest medicines” because they are given to healthy persons to prevent their contracting influenza in the future, for routine administration in pregnancy without requiring these drug products (Rho(D) serums and influenza vaccines) be evaluated for fetal safety to any safety standard* in animals and/or humans, as the “Pregnancy Class C” designation in their labeling 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 the FDA’s statements, the petitioners urge the Agency to immediately require the manufacturers of Thimerosal-preserved biologicals, as well as the makers of any drug product that uses Thimerosal in the process that produces that drug product, to:

- Comply with **21 CFR § 610.15(a)**, and
- Prove that their finished drug formulation is “sufficiently nontoxic ...” by using SJL/J mice and/or female (NZB x NZW)F1 (ZBWF1) mice and their offspring as animal models because these animal models have clearly been proven their “*ability to detect rare toxicities, or specific toxicities that may occur in a human*

^{Let-6} See www.fda.gov/oc/initiatives/criticalpath, Critical Path Initiative, **69 Federal Register** 21839, April 22, 2004).

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).”

First, the “SJL/J mouse” and the “female (NZB x NZW)F1 (ZBWF1)” mouse animal models:

- Exist and
- Are, *or seem to be*, appropriately predictive of Thimerosal toxicity in susceptible humans.

This the case because these animal models have produced symptoms, behaviors, and brain morphology changes for low-dose Thimerosal exposure which match those seen in mercury poisoning.

Thus, the petitioners must respectfully reject the FDA’s 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, the FDA is attempting to:

- Ignore the “elephants in the room” (“*adequate and relevant models*”) that the “SJL/J mouse” and the “female (NZB x NZW)F1 (ZBWF1)” mouse animal models represent and
- Change the 2004P-0349/CP1 petition’s request from proof that the compound used as a mercury-based preservative, Thimerosal, is safe (“*sufficiently nontoxic ...*”) at the preservative level (or a lower level) as required by law into a lesser “*risk that a vaccine will cause neurological damage..., in humans*” requirement that does

not meet the applicable CGMP *minimum* for proof that these drugs are “sufficiently nontoxic ...” as required by **21 C.F.R. Sec.610.15(a)**, because these “animal” models have proven that there is a mercury-poisoning risk from Thimerosal-preserved vaccines dosed according to the 2001 US national childhood vaccination schedule.

Moreover, though, *by definition*, autism is a “cause unknown” disorder defined by symptoms exhibited, petitioners find that here the FDA seems to be: **a)** asserting that autism is the “result” of “*neurological damage*” or **b)** claiming that the “cause” of autism is “*neurological damage*” such as that induced 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.”

Petitioners find that the FDA is being knowingly duplicitous in its remarks here because neither Hornig et al. nor the petitioners have hypothesized that autoimmune diseases are “*an underlying cause of autism.*”

As the record clearly shows, only you have made such statements.

Factually, Hornig et al. and the 2004P-0349/CP1 petition 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 petitioners find that the FDA's "*hypothesis*" statement is clearly at odds with the facts and contradicts the statements actually made in 2004P-0349/CP1.

At best, the FDA's apparent knowing distortion of these facts indicates that you have again failed to "carefully read" the 2004P-0349 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 challenge the FDA's "*to the best of our knowledge*" statement, petitioners note that this statement has little to do with the actual claims asserted by Hornig et al. or the 2004P-0349/CP1 petition.

At best, the reader should ignore the FDA's statement because it does not address the issues actually raised by the 2004P-0349/CP1 petition, but rather speaks to a hypothesis fabricated by the "FDA" officials who crafted this letter, and not to issues that Hornig et al., or the petitioners, 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 petitioners find the FDA's conclusion is derived from a hypothesis that you have fashioned from "whole cloth" and is, therefore, non-responsive to the issue raised in the 2004P-0349/CP1 petition.

Factually, as 2004P-0349 has plainly asserted, the "SJL/J mouse" model has clearly been shown to be a potentially valid animal model for assessing the "neurotoxic hazard posed by" Thimerosal (49.55% mercury by weight) to the developing brain in susceptible individuals, at the preservative and lower levels of Thimerosal found in the formulations of vaccines and other drug products.

The FDA does have a valid basis to connect these mercury-poisoning findings to the outcomes observed for Thimerosal-induced mercury poisoning in developing humans because:

- a. As you admit and petitioners 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 that have been mercury poisoned by Thimerosal or other mercury-based compounds.

Since the preceding findings apply 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 may be used to:

- Establish a “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
- Establish the “no effect” level in susceptible individuals for Thimerosal or other mercury compounds used in medicine in order to ensure that only a “safe” (“sufficiently nontoxic ...”) 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 the drafters of the 2004P-0349/CP1 petition 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

- The 2004P-0349/CP1 petition has cited appropriate references as evidence that supports or, *as required by 21 CFR § 10.30*, purports to refute, the issues the 2004P-0349 petition raised,

the petitioners see no valid reason for the FDA to state:

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

Moreover, petitioners find that the “*references cited that report an increase in the autism rate*” do, *in fact*, support 2004P-0349/CP1 petition’s argument (paradigm), which, *in simplistic terms*, can be stated as:

“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.”

Further, petitioners observe that the isolated sections of the 2004P-0349/CP1 petition that the FDA is addressing here are sections presented

in the overall context stated in the heading on P-7 of the 2004P-0349/CP1 petition, “**A. Safety Not Proven,**” for Thimerosal, or other mercury-based compounds, in vaccines and other drugs.

Unfortunately, we find that FDA’s remarks address the sections cited 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.’”

“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.”

Because the 2004P-0349/CP1 petition used the rates of autism, and other neurodevelopmental disorders, as markers for the underlying mercury-poisoning caused and/or aggravated by Thimerosal in vaccines, the petitioners understand that, while properly interpreting them is not without challenge, these increasing rates are not that 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.’”

Petitioners 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 petitioners find 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 the FDA’s statement:

“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 2004P-0349/CP1 petition.

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

Since 2004P-0349/CP1 made no such claims here, the current petitioners are at a loss to understand the FDA’s justification for making this contextually non-relevant comment.

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

Since, in this section, 2004P-0349/CP1 made no assertions of “*a causal link between thimerosal and neurological disorders*”, the current petitioners are again at a loss to understand the relevance of this statement in what, *you claim*, is a discussion of pages “*P-37 to P-39*” of the 2004P-0349/CP1 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, petitioners note that:

- The 2004P-0349/CP1 petition makes no contention that “(T)himerosal in vaccines cause” [sic; causes] “autism” in the sections of the 2004P-0349/CP1 petition that the FDA is citing here, and
- The “*contention*” that the FDA finds problematic was enunciated by Congress in a report, 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 2003.³¹¹

Second, the current petitioners note that your “*given that the amount of thimerosal that children receive through vaccines has decreased dramatically*” assertion is not supported by any actual nation-wide U.S. vaccination-experience data of which we are aware or, *as far as we have been able to ascertain*, which the Secretary of HHS, the FDA, the NIH, or the CDC has provided, published, or cited.

Factually, the existing stocks of Thimerosal-preserved vaccines were not recalled and destroyed when the “reduced Thimerosal,” “trace Thimerosal,” and “no

³¹¹ 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.

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”³¹²) 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 “influenza” 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,
- Increasing the age range for children who could receive Thimerosal-preserved vaccines to “from 6 months of age to 35 months of age” and recommending these children receive 2 doses, a month apart in 2004,
- In 2006, increasing the age range for children who could receive Thimerosal-preserved vaccines to: “from 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, and,

³¹² 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). *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. ...”

- In 2007, increasing the age range for children in “risk” groups who could receive Thimerosal-preserved vaccines to: from 6-months to essentially 107+ months of age (less than 9 years of age), and broadening the “risk” groups for children, the Secretary and the CDC have *significantly offset* the drop, and rate of decrease, in the maximum level of Thimerosal exposure from vaccines, such that the effective (specific dose) maximum Thimerosal exposure has definitely not “*decreased dramatically.*”

Moreover, the FDA has taken no action to remove Thimerosal- or PMA- preserved eye drops, ear drops, or nasal sprays from the market, because, *as you have stated*, you “*believe*” these are “safe,” although you admit you have no rigorous toxicity studies that prove they are safe even for adults to take, much less for a new born or young child to receive.

Furthermore, based on the petitioners’ discussion of the specific dose (dose divided by the subject’s body weight) and its approximate impact on toxicity (**see** pages P-249 – P-250 of this citizen petition), petitioners find the actions of the FDA (to approve) and CDC (to recommend universal use) have actually, *in effect*, increased the maximum toxicity that some children may experience.

This is the case because you have knowingly approved, *in deliberate disregard for the absolute need for proof of safety to the fetus,*³¹³ the administration of Thimerosal-preserved inactivated-influenza vaccines to pregnant women.

Finally, petitioners 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.

³¹³ 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 reproductive toxicity safety testing is an absolute must for Thimerosal-preserved vaccines that are recommended for administered to pregnant women.

Moreover, as discussed on pages P-280 and P-281 of this review, the valid data points³¹⁴ in the article by Fombonne et al.³¹⁵ 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.

Finally, in epidemiological studies conducted by Geier and Geier^{316,317,318} using CDC-recognized methodologies, these published peer-reviewed 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.

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

First, petitioners again note that, contrary to the FDA’s repeated attempts to mischaracterize the 2004P-0349/CP1 petition as arguing, as you state, “*thimerosal in vaccines cause*” [sic; causes] “*autism,*” the 2004P-0349/CP1 petition simply asserts that the evidence is clear 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*

³¹⁴ See the CoMeD document “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’]” posted at: http://www.mercury-freedrugs.org/docs/060827_PGK’sCmmnts_CanadianEpidemioStudy_Pediatrics-Full-b.pdf.

³¹⁵ 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.

³¹⁶ 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.

³¹⁷ 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].

³¹⁸ 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), 401-413.

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, petitioners note that the isolated section of the 2004P-0349/CP1 petition that you are addressing here is a section presented within the overall context stated in the heading on P-7 of the 2004P-0349/CP1 petition, “**A. Safety Not Proven,**” for Thimerosal, or other mercury-based compounds, in vaccines and other drugs.

Thus, petitioners find that your remarks address the section you cite here without addressing said section in the context in which it was 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 petitioners have, as *the FDA should have*, addressed and rebutted the Agency’s generally unsupported comments in that referential context of “**Safety Not Proven**” from 2004P-0349/CP1’s viewpoint – giving a mercury-containing medicine whose safety has not been proven to the applicable “sufficiently nontoxic ...” CGMP *minimum* to anyone mercury poisons them to some degree.

“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.”

Petitioners find that, *in the context of the lack of proof of the safety of Thimerosal in vaccines*, your statements accurately reflect the assertion made in 2004P-0349/CP1 and the references cited to support the statements made.

*“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, 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, ...”

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.”

Therefore, this research actually 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 petitioners 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 dietary and mercury-related medical history to find their matched controls

so that they might study these groups to elucidate, *for similar 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 mercury exposure history, it is clear that these researchers were principally interested in determining the effect of mercury excretion on the severity of the neurological effects.

Because differences in susceptibility to mercury poisoning among members of the population is one of the key issues that the 2004P-0349/CP1 petition raised, petitioners recognize that this study was properly included because it obviously supports that contention.

Therefore, the current petitioners 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 was not the level of mercury exposure but the differences in the level and pattern of mercury excretion that differentiated 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, petitioners note you failed to report or to address the study’s 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 is clear to the petitioners that this study of children established (proved) the existence of both: **a)** variable susceptibility to mercury-poisoning-related neurological impairment in humans and **b)**, *for those who exhibited obvious adverse clinical “neurological effects”* – those in the test group, a roughly 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, these issues do not detract from their finding that there are significant “mercury elimination” differences between: **a)** those children that do not have evidence of adverse clinical “neurological effects” (the control group children) and **b)** those children who were exhibiting adverse clinical “neurological effects” with respect to each group’s excretion of mercury in their hair.

This mercury exposure would have included a significant contribution from Thimerosal-preserved vaccines that these children received

This significant vaccine-related mercury exposure occurred because these children, who were fully vaccinated, were born between 1985 and 1999, a period 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 excretors. In general, the level of mercury excreted in their hair tracked the number of amalgam fillings their mothers had during pregnancy (probably from “methylmercury” they had accumulated from their mothers during gestation) with an offset that was probably related to the excretable circulating 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 petitioners note that you have fabricated the hypothesis you state here because it is not the working hypothesis that, *at the end of their introductory remarks*, the researchers *clearly* stated 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.”

The study's 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, some of the mercury in each subject's body, control and test, remains there for significant periods (decades) and, *based on other studies*, that "retained" mercury is toxic to the body.

Since the article does not contain the phrase, "*mercury burden*," or even contain the words "*bioactive*," "active," or "activity" and, *as far as the petitioners can ascertain these topics were neither germane to this study nor addressed by it*, we find that the hypothesis the FDA states here is an unseemly "whole cloth" fabrication on the FDA's part – a fabrication that: **a)** has no validity and **b)** cannot be reconciled with the actual hypothesis tested or 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 is *technically* true, the petitioners note that so is the following alternative 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."

because, based on the findings of this study, there is no direct 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, petitioners, *viewing this data in the light of the existing body of pertinent research*, find:

- The study's findings have probably established 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
- 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.

[Note: In contrast, as petitioners discussed earlier, the urine porphyrin profile analysis (UPPA) test has been proven, for several decades, to be a valid marker for: **a)** determining whether or not a person is mercury poisoned and **b)** estimating the current level of mercury poisoning in humans. If the FDA believes that establishing "*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*" is a critical need, then the petitioners note that an appropriate study using the UPPA test to estimate the level of mercury poisoning coupled with testing the levels of mercury in first-haircut samples and appropriately neurological assessments should allow the Agency to address its concerns and would suggest that the FDA commission the requisite study.]

Therefore, this study has clearly established that:

- There is an individual (genetic) variability component that, *for a similar general level of mercury exposure*, seems to separate those who have neurological injuries from those who do not, and

- Within those who have some clinical level of neurological injury, there was a general inverse relationship between the low level of mercury excreted in their hair and the severity of their clinical neurological injury.

Finally, as the 2004P-0349/CP1 petition 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 petitioners find that you have accurately 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, consisting of some fully vaccinated children with no evidence of a clinical neurological impairment and other 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.”

The petitioners find that the 2004P-0349/CP1 petition offered this paper as further proof of their assertion that, *in general*, the retention and excretion of mercury on children diagnosed with an ASD is different than the retention and excretion of mercury in 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, petitioners observe that this study apparently confirms the

2004P-0349/CP1 petition's assertion that those children, who have neurological damage that manifests 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 be skewed in the direction that most of the children with autism excrete little mercury."

Here, the petitioners find, absent any segregation of the children with autism from the ASD group evaluated, 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 DSM 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 petitioners agree that the FDA has accurately presented 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 2004P-0349/CP1 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, 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” is not germane to the issue being addressed at this point in 2004P-0349/CP1.

Moreover, because those with diagnosed clinical neurological injury are typically found to have “impaired” ability to detoxify themselves from a bolus dose of a mercury-containing compound and excrete the “mercury-containing” metabolism products 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), this “mercury metabolism difference” is an issue that: **a)** the paper addressed and **b)** the FDA somehow failed to notice, much less , address.

Therefore, because these remarks do not address the issues raised by the 2004P-0349/CP1 petition here, petitioners 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, the petitioners find that you are either ignoring the reality that the federal government: **a)** has *knowingly* permitted hundreds of thousands of healthy children to be injected with several courses of Thimerosal-preserved vaccines that lacked the required proof that they were “sufficiently nontoxic ...”, resulting in their being mercury-poisoned by their inoculations, or **b)** is *knowingly* “in denial” as profound as the injuries these children have suffered as a result of your “being asleep at the switch.”

The mercury poisoning that these mercury-susceptible children have suffered, and, *in most cases*, are still suffering, is so extensive that they exhibit the classic symptoms of subacute mercury poisoning.

These mercury poisoning symptoms, which are essentially the same as those used to diagnose autism³¹⁹ or other neurodevelopmental disorders and behavioral problems, are considered “causeless,” by the healthcare establishment *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 [proven] for mercury exposure in any baby much less in “susceptible individuals”)*.

Thus, we find that your rhetoric here attempts, *if nothing else*, to disregard and disrespect 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 C.F.R. § 610.15(a)** that such “shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient.”

Second, the petitioners note that, as we have already established (**see** pages P-236 through P-254 in this citizen petition), contrary to your “*Given*” assertion 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,*” the maximum level of Thimerosal today’s child receives by age 5, *given the current national childhood vaccination program’s recommendations*, 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 the mid-1990s.

[Note: Of course, this calculation does not factor in other mercury-containing prescribed and over the counter pharmaceutical products (e.g., eye and ear drops, nasal sprays, and other drug products), which remain on the market without any warning label being attached or any opportunity of informed consent being given.]

³¹⁹ 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.

Moreover, as the CDC has recommended since 2002, *when a pregnant woman is vaccinated with a Thimerosal-preserved influenza vaccine, the 50-µg dose of Thimerosal the pregnant woman receives may (depending on the size [weight] and developmental stage of the fetus when she is inoculated) be as toxic or more toxic to that unborn child than the post-natal Thimerosal-preserved influenza vaccines which the child may be administered, according to the current U.S. childhood vaccination schedule, from age 6 months to age 60 months.*

Since recent studies have again confirmed that the inactivated-influenza vaccines are *not* effective in preventing children³²⁰ or, *for that matter*, the general public³²¹ from getting or spreading influenza, petitioners conclude that the Secretary's continuing approval of the marketing of influenza vaccines is contrary to not only the clear requirements for proof of safety but also the expectation that these vaccines are effective.

This is the case because, *based on decades of U.S. population experience*, said influenza vaccines are not truly effective in preventing those inoculated from getting or spreading influenza.

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"*³²² to *"toxicity"* without addressing the critical difference between:

- A long-term accumulation of mercury from environmental sources having much

³²⁰ 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.

³²¹ 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.

³²² 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.

lower levels of mercury (typically, sub-ppm levels) and which are mostly from elemental mercury and inorganic mercury ingested, and

- Bolus doses of drug formulations (e.g., mercury-containing vaccines, eye and ear drops, and nasal sprays) containing 10 to 1000 times the readily available organic mercury level as other background organic-mercury sources (including protein-bound methylmercury species found in the fish that humans ingest) injected into and rapidly dispersed in the human body.

Petitioners find that the Agency's transparent attempt to distort these toxicological realities is beneath contempt.

In simplistic terms, *using the FDA's "Tylenol" illustration 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 to 1000 doses of that Tylenol all at once ("bolus dosing").

Petitioners observe 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 contained in a vaccine is significantly more likely to mercury poison a child than the typical less than the 0.0 µg to 0.2 µg dose of inorganic mercury he or she may ingest daily from drinking U.S. potable water.

Hopefully, any reader will, *as we have*, critique and reject your attempt to mislead here, as well as question your attempt to defend the unnecessary addition (*because there are other compounds [e.g., 2-phenoxyethanol], which are not the bioaccumulative*

teratogen and mutagen that Thimerosal is, that vaccine makers can and do use as preservatives) of a highly toxic substance with bioaccumulative toxic metabolites, Thimerosal, to a vaccine formulation at levels more than 5,000 times higher than the “least-toxic level” for Thimerosal established when the 2004P-0349/CP1 petition was filed³²³ (2004P-0349/CP1 petition’s endnote 6.A.3) and more than 100,000 times higher than the current established “least-toxic level” observed for Thimerosal.³²⁴

“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 14 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).”

Petitioners find that the Agency has accurately stated:

- a. The preservative issue, “Thimerosal in the Current Amounts is Insufficient to Qualify as a Preservative,” in the title, and
- b. The findings reported, *“the manufacturer’s preservative effectiveness tests showed that at 4°C, 4.5% of the challenged Streptococcus survived 14 days after inoculation into a multi-dose DTP vaccine vial,”* in its narrative here.

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>

³²³ 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.

³²⁴ Parran DK et al. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. *Tox Sci* 2005; **86**(1): 132-140.

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 “ $22.5 \pm 2.5^{\circ}\text{C}$,” “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 the FDA states here that the researchers found “*4.5% of the challenged Streptococcus survived 14 days after inoculation into a multi-dose DTP vaccine vial*,” 45 times the USP’s limit.

Because: **a)** the Agency cited no studies or other evidence to overcome the clear evidence in this reference and **b)** 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 2004P-0349/CP1 petition 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*, 0.01% Thimerosal in said lot of vaccine did 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.³²⁵ 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 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

³²⁵ 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.

preservative to provide protection, *until the vial's contents are used up*, to prevent needle contamination from contaminating the vial.

Based on these researchers' statements, Thimerosal is not effective in preventing short-term needle contamination of a vaccine vial by this common pathogen.

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

First, the petitioners find 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 relevant to the issue of meeting the USP's definition of an effective preservative – which, *according to FDA officials*, was, *and is currently*, a prerequisite for a compound's being used as a preservative in a vaccine formulation,
- Nothing prevents all U.S.-market vaccines from being packaged in a single-dose presentation that does not require the addition of any preservative, and
- *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)**, the Secretary of HHS, and the FDA acting on the Secretary's behalf, should have started banning the use of preservatives in all childhood vaccines in December of 1987 when this statutory mandate became effective because banning preservatives definitely lowers adverse reactions.

Additionally, the following are a series of historical studies that, *though they are readily available*, **a)** the FDA has apparently failed to consider and **b)** clearly establish

that Thimerosal, at a level of 0.01%, or lower, in a biological product formulation, is less than effective as a preservative:

1. A 1943 **JAMA** publication that questioned 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 finding 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...”³²⁶

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

³²⁶ Anonymous. Mercurials as ‘preservatives.’ *J. Am. Med. Assoc.* 1943; 122: 1253.

humoral components of the animal body, but there is also the possibility of sensitization.”³²⁷

3. Engley (1950) of the Biological Department, Chemical Corps, Camp Detrich published an evaluation of mercurial compounds as antiseptics.³²⁸ 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 (Green 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) presented a paper to the 42nd midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago, Illinois.³²⁹

There, 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

³²⁷ Morton HE, North LL, Engley FB. The bacteriostatic and bactericidal actions of some mercurial compounds on Hemolytic streptococci: in vivo and in vitro studies. *J. Am. Med. Assoc.* 1948; 136:37-41.

³²⁸ Engley FB. Evaluation of mercurial compounds as antiseptics. *Ann. N. Y. Acad. Sci.* 1950; 53: 197-206.

³²⁹ Engley FB. Mercurials as Disinfectants: Evaluation of Mercurial Antimicrobial Action and Comparative Toxicity for Skin Tissue Cells. Chicago, IL: 42nd Mid-Year Meeting of the Chemical Specialties Manufacturer's Association (1956).

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 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, petitioners underscore the reality that, *with respect to the toxicity experiments he completed in the 1940s*, Engley found Thimerosal was *lethally* toxic to human tissue-culture cells at a Thimerosal concentration of about 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 reported that five recommended strains, as well as three strains isolated from vaccines, were used as test strains.

They found that vaccines preserved with Thimerosal did not fully meet the requirements for a vaccine preservative according to the criteria for an effective preservative that were established in USP XIX.³³⁰

6. Evaluating the antimicrobial action of various preservatives for vaccines, Lowe and Southern stated in 1994.³³¹

“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 compared the antimicrobial activity of “phenoxyethanol” (also called 2-phenoxyethanol) with Thimerosal in diphtheria, tetanus, and pertussis (adsorbed) vaccine in a series of experiments.

Based on these studies, they noted:

“Both 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...”

“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, petitioners again note that, *by your own admission*, Thimerosal does have established adverse reactions, including “*hypersensitivity.*”

In addition, at the start of the first day of the October 1999 “Lister Hill” workshop on “Thimerosal in Vaccines”,³³² *attended by FDA officials*, Dr. Jerome, Klein from the Boston University School of Medicine, stated in his opening remarks:

³³⁰ Hekkens FE, Polak-Vogelzang AA, Kreeftenberg JG. The antimicrobial effectiveness of some preservatives in inactivated human vaccines. *J Biol Stand* 1983; 9: 277-285.

³³¹ Lowe I, Southern J. The antimicrobial activity of phenoxyethanol in vaccines. *Lett Appl Microbiol* 1994; 18: 115-116.

“The most frequent adverse events that have been identified with thimerosal are those of a hypersensitivity reaction, papular or vesicular disruptions.”

Thus, in addition to “*hypersensitivity*,” medicine apparently recognizes “papular or vesicular disruptions” as “frequent adverse events” – clearly indicating that the Agency’s statement here is either less than accurate or *knowingly* misleading.

Second, as the FDA knows and we have established, *in worst-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 petitioners actually reviewed the studies you cited, we found a significant number do provide peer-reviewed scientific epidemiological evidence showing a statistically significant increased risk for some neurodevelopmental disorders following exposure to the Thimerosal-containing vaccines.

Based on all of the preceding, petitioners are compelled to find that the FDA has again failed to provide or cite, any scientifically sound and appropriate toxicity studies to justify the presence of Thimerosal at “preservative” levels, given the unmet and unchallenged legal requirement to prove that the level of Thimerosal is safe to the standard “sufficiently nontoxic ...”

³³² 11-12 August 1999 (Confidential Transcript) The National Vaccine Advisory Committee Sponsored Workshop on Thimerosal in Vaccines convened by the US Department of Health and Human Services, the Public Health Service, and the Centers for Disease Control and Prevention (National Institutes of Health, Lister Hill Auditorium, Bethesda, Maryland)

“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.”

We accept your statements as being valid.

However, petitioners 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 in your duty to ensure that the manufacturers prove that such drug products are “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, petitioners find: **a)** 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, and **b)**, therefore, you have not discharged your mandated “reduce adverse reactions” duty, as set forth in **42 U.S.C. 300aa-27(a)(2)**, in a manner that complies with said statute because anaphylactic reactions, *known to be caused by Thimerosal in sensitized individuals*, are not dose dependent.

“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 petitioners’ relevant comments on page P-302 through P-304 of this citizen petition.

Since you have failed to provide any evidence or publications to support your stated views, we must conclude that the 2004P-0349/CP1 petition’s evidence-supported views are valid, while your statements here again appear to be simply unsupported rhetoric.

“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 2004P-0349/CP1 petition presented other studies that address the consequences of Thimerosal exposure in cells, animals, and humans, petitioners fail to see the relevance of this heading or the discussion which follows it, since we have established that the use of Thimerosal, *at any level*, is “**not proven safe.**”

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

Thus, in light of the fact that: **a)** the requisite long-term scientifically sound and appropriate toxicity studies have not been reported or, *to our knowledge*, conducted, and **b)** you have not presented any such evidence, petitioners find that that the Secretary and responsible FDA officials have failed to ensure that Thimerosal-preserved vaccines met the clear “sufficiently nontoxic ...” requirement *minimum* set forth in **21 C.F.R. § 610.15(a)**, *as required by law*, before (as

affirmed in 1988 in *Berkovitz v. U.S.*³³³), at a minimum, you can legally exercise your administrative discretion to license or approve any Thimerosal-preserved 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 be 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 petitioners note you do not deny that Thimerosal is:

- Neurotoxic at levels below 0.02 ppm, as papers cited in the 2004P-0349/CP1 petition support, or at levels below 0.001 ppm, as Parran et al. established in their 2005 paper,³³⁴ or
- A teratogen, mutagen, carcinogen, immunogen and autoimmunogen as the 2004P-0349/CP1 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 LD₅₀ (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 2004P-0349/CP1 petitioners wrote (on page P-15 of said petition):

“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,’”

³³³ Kevan Berkovitz, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., *Petitioners, v. UNITED STATES*. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

³³⁴ Parran DK et al. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. *Tox Sci* 2005; **86**(1): 132-140.

it is obvious to the current petitioners that this paper was cited as proof that the mercury administered (with underlining added to highlight the key issues):

- Led to “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 the 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) so that they could maintain and conveniently study these animals while ensuring that they would obtain observable effects on the animals studied 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.”

While the FDA’s artfully crafted statement here is technically correct, the petitioners find that these concentrations are also only 1 to 10 times the Thimerosal level: **a)** in the “*currently available*” Thimerosal-preserved “*childhood vaccines,*” including the ineffective inactivated-influenza vaccines, that are currently being routinely administered to children and pregnant women, or **b)** in almost all of the many U.S.-

licensed doses of the Thimerosal-preserved vaccines given prior to 2000.³³⁵

Therefore, petitioners, as any vaccine-knowledgeable "person" should, 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."

The significance of the findings cited in the 2004P-0349/CP1 petition is clear to the petitioners because:

- The Thimerosal-preserved influenza vaccines are still recommended 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,

These findings are obviously significant in the context of Thimerosal-preserved childhood vaccines that:

- Were ubiquitously used in the U.S. until 2000, *even though the Scandinavian countries and Canada removed them from their recommended "universal" childhood vaccination schedules in the mid-1990s*, and
- Include the ineffective inactivated-influenza vaccines and other Thimerosal-containing vaccines currently approved for use in children and pregnant women.

Finally, the importance of the FDA's "*...the significance of these findings in the context of trace amounts of thimerosal contained in today's pediatric vaccines is unclear*" remark is that its stated conclusion "*is unclear*" is an admission that the FDA does not know that the "*trace amounts of thimerosal contained in today's pediatric vaccines*" are safe.

³³⁵ Petitioners note that, according to internal CDC emails, out patients at Bethesda Naval Medical Center, *where the families of our Presidents and members of Congress are treated*, were being given reduced-Thimerosal vaccines in 1998.

“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 2004P-0349/CP1 petition, which mistakenly stated that the researchers used the 2001 schedule, the current petitioners find that, nonetheless, you missed the key point highlighted by this paper, 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.”

Petitioners find that, using the preceding doses and the EPA’s overly optimistic “guideline” of 0.1 µg/kg/day for dietary mercury intake in children, the injected dose of

Petitioners’ Table 4 Thimerosal “Bolus Dosing”: Doses Exceeding EPA RfD

	Child’s Age At Inoculation				
	Birth	2 months	4 months	6 months	18 months
Dose (µg of mercury)	12.5	62.5	50	62.5	50
Weight in kg (pounds) required for specific dose of 0.1-µg Hg/kg	125 (276)	625 (1,378)	500 (1,102)	625 (1,378)	500 (1,102)
5 th to 95 th 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 5 th percentile child	47.7	149.8	90.6	95.6	“49.5”
Exposure multiple for 95 th 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 the 15 months’ values published in the Geier and Geier paper.

mercury each child received on each date is a bolus dose that exceeds this EPA "guideline" by a factor of at least 10 times the level dosed, divided by the child's weight in kilograms at a given time point.

As "**Petitioners' Table 4**" on the previous page clearly shows, the dose received is obviously more than 10 times the EPA "guideline" (0.1 µg/kg/day) at each inoculation age.

This table's values clearly demonstrate the reality that each dose of vaccine significantly mercury poisons the child inoculated for some time after inoculation.

"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, petitioners 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: a) the Thimerosal dosed provided mercury exposures that exceeded, *at the time of inoculation*, the EPA "Rfd" (for

ingested dietary mercury) of 0.1 µg Hg/kg/day for some period of time or **b)** the Agency recently adopted this value as the FDA's level of concern for mercury in drugs given to developing children even though it is generally accepted today that this EPA value is at least twice,³³⁶ and, *more likely*, ten or more times too high for injected mercury doses.

Third, recent studies have clearly shown that that EPA "RfD" should be about an order of magnitude lower (based on evidence that:

- a. The actual level of mercury exposure in the populations studied was significantly less than previously estimated,³³⁷ and
- b. The finding that mercury excretions rates in hair are not the same:
 - i. In different populations,³³⁸ or
 - ii. Within individuals in a given population [as discussed in Holmes et al.³³⁹]).

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,"

petitioners note that, *though the half-life times reported for hair have not been confirmed, the paper by Burbacher et al.³⁴⁰ has shown that, for changes in blood levels following mercury-compound dosings in the baby monkey groups studied, the pattern for ingested*

³³⁶ Grandjean P, Budtz-Jorgensen E. Total imprecision of exposure biomarkers: implications for calculating exposure limits. *Am J Ind Med*. 2007 May 9; [Epub ahead of print]

³³⁷ Gosselin NH, Brunet RC, Carrier GT, LeBouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data. *J Exposure Anal Environ Epidemiol* 2006, 16(1): 19-29.

³³⁸ Canuel R, Boucher de Grosbois S, Atikessé L, Marc Lucotte M, Arp P, Ritchie C, Mergler D, Chan HM, Amyot M, Anderson R. New Evidence on Variations of Human Body Burden of Methylmercury from Fish Consumption. *Environmental Health Perspectives* 2006 Feb; 114(2): 302-306.

³³⁹ Holmes AS, Blaxill MF, Haley BE. Reduced levels of mercury in first baby haircuts of autistic children. *Int J Toxicol* 2003; 22: 277-285

methylmercury hydroxide is similar to the pattern projected for the authors' "no excretion" model (see footnote 340's Figure 2), while the pattern for the injected Thimerosal is similar to the pattern projected by the authors' "adult excretion" model (see footnote 340's Figure 5).

Though Burbacher et al. explained the differences they observed as resulting from differences in the mercury-based compound dosed, petitioners find that the differences Burbacher et al. observed are probably as attributable to the differences in the mode of administration (ingestion [oral gavage] versus injection) as they are to 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.

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 seems appropriate.

Petitioners find 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 modeling the decay of the mercury levels in either primate circulatory systems or primate brains.

Finally, petitioners sadly note:

- a. The half-life for "inorganic mercury" in the brains of human "mercury excretors" has been found to be on the order of two decades³⁴¹ and

³⁴⁰ 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.

³⁴¹ a. 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.

b. Owhadi H, Boulos A. Bistable equilibrium points of mercury body burden. *Quantitative Biology* 14 July 2006. <http://aps.arxiv.org/abs/q-bio/0606024>.

- b. To date, no valid estimates have been published for the half-life of “inorganic mercury” in the brains of “non-excretors” who have not been given any type of “chelation therapy,” designed to reduce the bioburden of mercury in all tissues, including the brain.

Based on the reported half-life data, it is clear to the petitioners that any prenatal or postnatal vaccine-derived mercury that is “converted” in the brain into “inorganic mercury” will, *absent chelation therapies designed to remove it*, exert that inorganic mercury’s proven toxic effects throughout childhood and beyond.

This fact alone should be reason enough to immediately ban all uses of any mercury compound in medicine.

“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.”

First, the petitioners note that this reference was probably 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 2004P-0349 petition states:

“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, petitioners observe that, though you claim to understand “*there is a need to further study this important ingredient (i.e., thimerosal) with regard to both benefits, and*

c. Aschner M, Aschner JL. Mercury neurotoxicity: mechanisms of blood-brain barrier transport. *Neurosci Biobehav Rev.* 1990; 14(2): 169-176.

potential associated risk,” the Secretary, and the responsible officials in the FDA and the NIH 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 Thimerosal’s safety (freedom from “*risk*”), and/or
- Failed to require the vaccine makers, *as required by law (21 C.F.R. § 610.15(a))*, to perform and report the requisite toxicity studies to prove the preservative in their Thimerosal-preserved vaccines was “*sufficiently nontoxic ...*,” *before the licensing/approval of any new Thimerosal-containing vaccine formulation or continuing the licensing/approval of all existing Thimerosal-containing vaccines*,

even though more than three-quarters of a century has passed since Thimerosal was first used as a preservative in biological products, and, *for the second bullet*, more than a quarter of a century has elapsed since the cited regulation became CGMP law.

In that regard, *in spite of having been repeatedly reminded about this legal requirement in the 2004P-0349/CP1 petition since August of 2004*, the FDA has continued to license new Thimerosal-preserved vaccine formulations, including, on Thursday, 5 October 2006, FluLaval®, a Thimerosal-preserved (0.01%) inactivated-influenza-virus vaccine and, in 2007, an avian influenza vaccine, without, *as far as we can ascertain*, requiring each manufacturer to conduct and submit said toxicity studies to prove safety (a prerequisite for assessing “*risk*” under **21 C.F.R. Sec. 600.3(p)**) despite a published retrospective “in use” study³⁴² clearly establishing, *based on published U.S. governmental and other public data*, that inactivated-influenza-virus vaccines are not effective in preventing: **a)** those who have been inoculated from

³⁴² 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.

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 the FDA has 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 C.F.R. § 610.15(a),*

even though required to do so by the limits on your administrative discretion affirmed by the U.S. Supreme Court’s 1988 unanimous decision in *Berkovitz v. U.S.*

Moreover, **there is no scientific proof proving that Thimerosal, *at preservative levels, poses no risk of significant neurological injury to 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%³⁴³ 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.

This practice is even more perplexing because, *as far as we can ascertain*, that inoculation conveys little or no long-term immunity to the infants vaccinated at birth.

Given that: **a)** almost no babies are at risk of contracting hepatitis B at birth and **b)** the hepatitis B vaccine administered at birth is not effective in immunizing them from getting hepatic B, the petitioners are compelled to ask you:

"Given:

- There is no universal risk to newborns contracting hepatitis B,
- An effective rapid hepatitis B test exists to identify '*hepatitis B-infected mothers,*'
- 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 little or no protection to newborns,

what incentive, other than providing additional revenue for the vaccine producers, and the healthcare providers, could have caused the Secretary of HHS, through the CDC, to recommend giving the Thimerosal-preserved hepatitis B vaccine to all newborns?"

Third, petitioners find that your:

³⁴³ <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%.

“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 American children born in the 1990s who were injected with the Thimerosal-preserved hepatitis B vaccine and the hundreds of thousands that may have been harmed by their “birth” 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 2004P-0349 petition, which here stated:

“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 petitioners note that even though this data was for samples taken 2 to 4 days after inoculation, the levels of the mercury in the infants’ blood streams were still *significantly* elevated.³⁴⁴

Since the CDC 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 some extent*, to the mostly Thimerosal-preserved influenza vaccines their mothers have received.

This increase in preterm deliveries is appropriately associated with vaccine-delivered mercury because:

- The level of mercury in U.S. air, food, and water has not significantly increased,

³⁴⁴ Presuming, based on Burbacher et al., the half-life of injected “organic mercury” is about 7 days, the peak levels could have been up to a third higher than the values found days after the inoculation.

- Pregnant women have been warned of the risk of mercury in fish and, in many cases, have 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 sources other than vaccines.

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,³⁴⁵
 - 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 0.54 ± 0.79 ppb versus 0.04 ± 0.09 ppb for the term infant,
- the petitioners 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 female (NZB x NZW)F1 (ZBWF1) mouse, and, *for reproductive studies*, the rat strain used in the reference Goncharuk study, in which the test animals are known to be susceptible to the toxic effects of Thimerosal before approving any Thimerosal-preserved vaccine for use – much less approving ineffective ones,³⁴⁶ and

³⁴⁵ Goncharuk GA. Experimental investigations of the effect of organomercury pesticides on generative functions and on progeny. *Hyg. Sanit.* 1971; 36: 40-43.

³⁴⁶ Geier DA, King PG, Geier MR. Influenza Vaccine: Review of effectiveness of the U.S. immunization program, and policy considerations. *JAPS (Journal of American Physicians and Surgeons)* 2006 Fall; 11(3): 69-74.

- Your failure to require the proof of safety required by **21 C.F.R. § 610.15(a)**.

“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 petitioners do not dispute the factual information you stated here concerning the Thimerosal arm of the study by Burbacher et al. that the FDA is citing.

“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, petitioners find that your statement is not accurate.

Factually, including the 25-µg dose of mercury from a Thimerosal-preserved “flu”-vaccine shots 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 used at 7 months.

Thus, the FDA has apparently *knowingly* underestimated the nominal maximum exposure in the earliest, and most critical, period of life for babies born after 2005 by: **a)** a factor of about 9 (before 6 months), and **b)** a 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, the petitioners 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 1999 childhood immunization schedule, would have received by two years of age.

Third, we find that the cumulative exposure level used was also lower than a child would have received by 2 years of age.

Moreover, we also note that, *contrary to the usual design of toxicity assessment*, the study did not, as it should have, include, *at a minimum*, a 10-X exposure arm to ensure that toxic effects, *if any*, might be observed because the study period was much shorter than the *relative* “one to three” years needed to see significant levels of clinical harm in the Thimerosal-treated monkeys because mercury is known to be a slow and insidious poison for which, *at sub-acute dosing levels*, the onset of clinical symptoms may be delayed for a considerable period of time.

“These levels are significantly lower than the one used in the study by Burbacher, et al.”

Petitioners note that, *after appropriately correcting your claimed values*, the current levels of *maximum* Thimerosal exposure are “*not significantly lower*” than the levels used in the study by Burbacher, et al.

We also note that your response here has *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 Thimerosal-preserved influenza vaccines – vaccines that are, based on their in-use history, 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 petitioners 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.

Moreover, we note that, since the published Burbacher et al. study did not focus on the effects observed from the dosing but only on its redistribution in the test animals, the FDA’s statement here is also misleading.

Again we observe, your statement here supports, *among other things*, the petitioners’ contention that the safety of Thimerosal in vaccines has not been proven.

In fact, we are at a loss to understand what, *if anything*, this published study was actually designed to assess because:

- If the study were designed to validly assess the toxic effects of Thimerosal, then its failure to: **a)** dose the test animals at higher levels, 10X, or 10X and 100X the vaccine levels and **b)** 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 between the distribution of mercury from methylmercury hydroxide and that distribution from 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 to which it added the

Thimerosal to (instead, the researchers dissolved methylmercury hydroxide in water), and

2. To utilize the same route of administration for both of the 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 mercury-labeled compounds should have been used, and the animals' feces and urine collected and analyzed to show the rate at which the compounds cleared the animals; however, *if these studies were done, they were not reported.*
 - If the goal were to assess evidence of toxicological damage to the brain and other organs, then the researchers should have appropriately sectioned and stained the animals' brain and other 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, as published 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 the study's findings and observe, *in that regard*, the study succeeded.*

Again, petitioners find 2004P-0349/CP1 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 2005, after the 2004P-0349 petition was submitted) *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 brain in the range of 15 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 the FDA’s unsubstantiated (by documented study or recognized scientific references) views, the petitioners find that the studies cited in 2004P-0349/CP1:

- Are valid science and
- Do support eliminating all Thimerosal and other added mercury compounds from all products.

However, *notwithstanding that finding*, the petitioners note that under *Berkovitz v. U.S.*:

- Conformance to the explicit requirements of **21 C.F.R. § 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, *broadly defined in the United States of America*, as a human from viability 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. Sec. 262(a)(2)(A)** would require you to remove all other Thimerosal- and other-mercury- containing drugs from the market, unless 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.

The requirement that safety must be proven to the standard “sufficiently nontoxic ...” is compelling because, *for example*, 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, and the other mercury compounds used in drug products (typically, phenylmercuric salts) are similarly toxic.

Given the sub-ppm toxicity of Thimerosal and the other mercury compounds used in drug products, petitioners find these requirements cannot be met in any scientifically sound and appropriate toxicity study using an appropriate “mercury-poisoning-susceptible animal” model.

“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 al. (2002) (refer to endnotes 42-50).”

Here, petitioners find that the FDA has correctly stated the issue that 2004P-0349/CP1 raised here, and note that each of the listed references cited did make the statements that clearly support the recommendation stated in said petition.

“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, petitioners note that your comments failed to address the issue raised by 2004P-0349/CP1, which states:

"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.'"

Moreover, the excess toxicity observed was proven to be caused by the Merthiolate (a/k/a Thimerosal) and the level of Thimerosal, "0.01%," is the same level found in most Thimerosal-preserved vaccines.

Thus, *at a minimum*, this article clearly establishes that 0.01% Thimerosal in a vaccine formulation or in a saline solution, was significantly toxic to mice, at the dose given, shortly after that dose was injected.

Further, petitioners 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 2004P-0349/CP1, and **b)** there is also no data to suggest that the Thimerosal-preserved pertussis vaccine formulation, which shows a greater toxicity in mice than the no-Thimerosal formulation, does not also have a greater toxicity in humans.

Returning to the key issues raised in 2004P-0349/CP1, *since you have knowingly continued to license/approve Thimerosal-preserved childhood vaccines*, petitioners note that the somewhat lethal dose administered to the mice was only about 46 times the dose of mercury generally contained in the Thimerosal-preserved childhood vaccines

you have continued to license/approve – the very vaccines 2004P-0349/CP1 sought to remove from the market, unless their manufacturers could prove their vaccines meet the clear “sufficiently nontoxic ...” requirement of **21 C.F.R. § 610.15(a)** and, *for childhood vaccines*, you could 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 2004P-0349/CP1 issues:

- “... sufficiently nontoxic ...” as set forth in **21 C.F.R. § 610.15(a)**, and
- “Mandate for safer childhood vaccines” as set forth in **42 U.S.C. § 300aa-27(a)(2)**,

you will then do so in a manner that complies with the legal limitations placed on your administrative discretion as affirmed by the findings in *Berkovitz v. U.S.*

“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 ⁵¹Cr 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 petitioners 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 study 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:

“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 Merthiolate hypersensitivity reactions in humans, 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 plainly reveals:

- Merthiolate (another name for Thimerosal) in vaccines produces adverse reactions in humans,
- These researchers warned you to remove it from vaccines in 1980,
- You ignored their warning, and
- Because the requirement set forth in **21 C.F.R. § 610.15(a)** had become law in 1973, you were *knowingly* permitting vaccine makers to ignore this legally binding regulation's requirement to prove their Thimerosal-containing drug product formulations are "sufficiently nontoxic ...".

"Kravchenko, et al. (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, petitioners again observe:

- The burden of proof:
 - Is to prove safety,
 - Is directly the vaccine makers' non-dischargeable duty, and indirectly also your duty, and

- You have knowingly failed to require the requisite proof of safety under **21 C.F.R. § 610.15(a)** as you should have before licensing, *or continuing to license*, any Thimerosal-preserved vaccine or other biological product after 1973, if not before.

Second, you again have failed to provide any scientific evidence or references to support your dismissal of *in vitro* studies showing significant mercury 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”

Thus, as your answer *clearly* illustrates, the Secretary and FDA have *knowingly* ignored the scientifically sound advice provided by Kravchenko et al. and continued to act in a manner that does not appear to conform to the legal strictures within which you are required to operate.

“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 that were reached by the authors of the articles referenced here since, *overall*, they advised Thimerosal

should be removed from Thimerosal-preserved 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-dose injection preparations are undesirable and that preservatives should not be present in unit-dose preparations.”

In simple terms, Winship was recommending that the manufacturers of these drug products:

- 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 reported 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* ignored 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 C.F.R. § 610.15(a)**, you have knowingly continued to ignore this clear law until the present (e.g., licensing/approving the Thimerosal-preserved FluLaval inactivated influenza vaccine on October 5, 2006).

Finally, this article is important because, *on June 13, 1988*, the US Supreme Court unanimously affirmed, in *Berkovitz v. U.S.*, 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 finding 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 petitioners 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 scientists 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 possessed and submitted scientifically sound and appropriate toxicological studies to prove their product formulation was “sufficiently non toxic ...” (21 C.F.R. § 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 v. U.S.* and the applicable legal and statutory requirements that 2004P-0349/CP1 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 that particular groups of individuals, pregnant women and children 6 months of age and younger, should not receive any Thimerosal-containing product.

Yet, we find that you ignored this author’s recommendation and the supporting science and the applicable laws and statutes.

In fact, in 2002, the Secretary of DHHS not only did not protect pregnant women and young infants from the mercury-containing drug products on the market but also, *through the CDC*, began recommending that pregnant women and children 6-months to 23-months of age be given inactivated flu vaccines, including the Thimerosal-preserved vaccines, during the US influenza season.

This recommendation *significantly* increased the risk to adverse reactions in children (a knowing violation of **42 U.S.C. § 300aa-27(a)(2)**).

Moreover, *based on this research report*, this recommendation condoned the knowing violation of **21 C.F.R. § 610.15(a)** because neither you nor the Secretary of HHS possessed toxicological proof that Thimerosal in the Thimerosal-preserved influenza vaccines was “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient” – in this case, to the fetus, who continues to be exposed to up to 50 µg of Thimerosal when the fetus’ mother is inoculated with a Thimerosal-preserved flu vaccine, and to the young child, who is exposed to that dose or half that dose of Thimerosal.

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,³⁴⁷ who clearly established:

- a. You had no scientifically sound and appropriate proof of safety and
- b. There is a body of evidence and information indicating fetal harm from Thimerosal.

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.

Furthermore, *under Berkovitz v. U.S.*, you lack the administrative discretion not to:

- a. Comply with **42 U.S.C. § 300aa-27(a)(2)**, or
- b. Require CGMP compliance by the manufacturers with **21 C.F.R. § 610.15(a)**.

Therefore, *given the preceding realities*, you should have removed all the licensed/approved Thimerosal-preserved vaccines from the market in the mid-1970s

³⁴⁷ 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.

and stopped licensing/approving Thimerosal-preserved vaccines in 1973 or, after *Berkovitz v. U.S.*, no later than mid-1988, at the latest.

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 v. U.S.* and the applicable requirement *minimums* established by law for drug products containing Thimerosal or other added mercury compounds.

“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 petitioners 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 petitioners 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, Beverly 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.”

Thus, the petitioners find that, as asserted in 2004P-0349/CP1, the “FDA has not followed recommendations by researchers calling for an end to adding any amount of Thimerosal to vaccines and other biological products even though many of the cited articles provided clear evidence of Thimerosal’s toxicity.

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

Since you have failed to provide or cite any scientific evidence or studies to support your claims, the petitioners must reject your assertions because they are unsubstantiated.

In addition, we find your heading, “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 admit.

Likewise, we find your heading, “... Studies Cited are ... Inapplicable to Human Vaccines,” also contradicts factual reality because:

- Thimerosal, also known as “ethyl mercury thiosalicylate, 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
- After injection, processes in the human body convert much of 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 petitioners only agree that 2004P-0349/CP1 cited these articles