

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.

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  $\mu$ l per drop, the total daily exposure to mercury would be 0.25 mg/day or 5  $\mu$ g/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  $\mu$ g/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.

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.

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.

## **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  $\mu$ g/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). You have cited work done by Leong, et. al. (2001), in support of this statement. 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; however, the data do not prove that thimerosal in vaccines causes autism in humans, 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.

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 ( $\mu g$ ) of mercury per kg.” 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  $\mu g$  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).

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. 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. 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).

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. 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., adsorption), 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.

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 pain killer 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).

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.

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).

Havarinasab, et al. studied whether thimerosal induces a systemic auto-immune 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.”**

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

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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. 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. 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).

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. 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. 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.<sup>Let-6</sup>

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). 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. 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 autoimmune diseases, which you hypothesize are an underlying cause of autism. 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. 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.

<sup>Let-6</sup> See Critical Path Initiative, 69 Federal Register 21839, April 22, 2004

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

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. 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.” Furthermore, the reports did not address the causes of this increased prevalence and the issues and factors related to the etiology of autism. Notably, none of these reports establishes a causal link between thimerosal and neurological disorders as suggested by you. 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.

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

On pages P-19 to P-42 of your petition under your section “Clinical Evidence”, you have stated that “growing clinical evidence strongly suggests that many, if 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.

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.** 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.

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. 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. 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.

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.

As pointed out by the IOM (see 2004 IOM report), the range of mercury excreted was 0-59 with a mean of 4.1  $\mu\text{g}$  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. 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 [sic; is] unable to process, thus leading to higher mercury burden. 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. 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.

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).

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

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. 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.

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

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).

FDA wishes to comment on the findings of these papers, particularly as they relate to your argument. The purpose of the investigation by Gasset, et al. was to evaluate the effect of thimerosal in rats and rabbits when topically applied to the eye and when systemically administered because of observation that ophthalmic medications produce teratogenic effects. No fetal malformations were observed even when given at concentrations approaching the LD<sub>50</sub> (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.

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. Thus, the significance of these findings in the context of trace amounts of thimerosal contained in today's pediatric vaccines is unclear.

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.

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.

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.

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.

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

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

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).

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.

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 <sup>51</sup>Cr release from labeled cells. Because of data in the literature on binding of merthiolate to sulfhydryl (SH) groups of proteins, the authors suggest that if thimerosal binds to horse immunoglobulin,

it may reach a toxic level in the region of lymphoid cells. While data provide further evidence about the known in vitro cytotoxic effects of mercury, no direct evidence was provided in this paper that would support the conclusion of the authors.

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.

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 al. (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.

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.

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

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. Tryphona, et al. [*sic*] conclude that alkyl mercury compounds, if fed at low concentrations for long periods, were poisonous to swine. The authors were concerned with public health implications, especially when meat, liver, etc., of poisoned pigs are consumed by people. Magos, et al. compared the neurotoxicity and renotoxicity of alkyl mercury compounds in Porton Wistor rats. FDA acknowledges that alkyl mercury compounds, such as methyl mercury and ethyl mercury, especially when administered at high doses, are toxic; however, an extrapolation of the above data to infant exposure at far lower levels of thimerosal, and neurodevelopmental disorders, is problematic. For example, Tryphonas, et al., was concerned with consumption of parts of pig by humans derived from animals

exposed to certain threshold levels of mercury that may pose health hazards. In addition, in the study by Magos, et al., the cumulative dose administered to rats was 40 mg/kg which is >13000 times the cumulative dose that an infant less than 6 months of age would be exposed to (<3 µg) through administration of vaccines containing trace amounts of mercury.

Fagan, et al., analyzed samples of fresh and fixed tissues from infants with exomphalos treated by thimerosal application for mercury content. Results showed that thimerosal can induce blood and organ levels of organic mercury that were, as stated by the authors, in excess of the minimum toxic level in adults and fetuses. However, the authors note that “whether the levels reported are acutely toxic or capable of producing chronic neurological damage in the newborn infant exposed perinatally... is unclear.”

We note that the authors advise against the use of mercurial antiseptics for the treatment of exomphalos or for hospital use in general. We further note that the authors’ statement that equally effective and far less toxic broad-spectrum antifungal and antibacterial antiseptics were available in 1977 referred to **topical** antiseptics, and not to preservatives used in vaccine products.

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

FDA has also reviewed studies by Ashwood, et al., McGinnis, and Megson, which you cited (endnotes 61, 64, and 63). Ashwood, et al. (endnote 61) tested the hypothesis of a novel and characteristic enterocolitis in a subset of children with autism and gastrointestinal symptoms. The study did not examine the etiology of the enterocolitis in affected children. The authors stated that further studies are required to demonstrate potential links of these findings with disturbed cognition in autism. McGinnis (endnote 4) suggests that toxins known to cause gut injury be considered when looking for causes of autism and that “some specifics about autism should heighten interest in mercury.” He mentions that “ethyl mercury as a vaccine preservative may also inflict gut injury.” No data were presented or referred to substantiate these statements. Thus, a link between ethyl mercury and gut injury as a cause for autism is speculative. Megson, et al. (endnote 63) hypothesize that autism may be a disorder linked to the disruption of the G-alpha protein and suggests that this may be reversible by treatment with natural vitamin A. The paper mentions that pertussis toxin in the DPT vaccine leads to a G-alpha protein defect causing autism in genetically at risk children. The paper also speculates that live viral measles vaccines depletes children of their Vitamin A supply. FDA finds that the conclusions reached in this paper are speculative and do not support the theory.

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### III. PETITIONERS' LEGAL ARGUMENTS LACK MERIT

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

For the scientific reasons discussed above in Sections I and II, none of the actions and legal remedies you seek against vaccines or other products containing thimerosal are warranted. Therefore, we need not address your arguments about the scope of FDA's authority to take particular legal actions or to pursue particular remedies. Instead, we decline your request for those actions and remedies on the substantive grounds that the few vaccines and other legally marketed products that contain thimerosal are safe and that no action against those products based on their thimerosal content is appropriate.

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

At the end of the "Statement of Grounds" portion of your citizen petitions, you add two legal arguments as subsections B and C: "Violation Of Constitutional Right To Bodily Integrity" and "Violation of Other Civil Rights And Societal Tenants." Those two sections are not included among your Requested Actions, and you do not appear to be petitioning FDA to act on those claims. Nevertheless, FDA has the following responses to your arguments.

In subsection B (page P-45 of your petition), you cite *In re Cincinnati Radiation Litigation*, 874 F. Supp. 796, 810-811 (S.D. Ohio, 1995), *Albright v. Oliver*, 510 U.S. 266 (1994), and *Schmerber v. California*, 384 U.S. 757, 772 (1966), to argue that the Due Process Clause of the Fourteenth Amendment creates a substantive due process right to be free of state-sponsored invasion of a persons bodily integrity. You then state that "by authorizing the manufacture, distribution, and, most importantly, the use of vaccines and other drug and biological products containing neurotoxic ingredients, including, but not limited to, Thimerosal..." the government is "responsible for performing uncontrolled involuntary experiments on susceptible pregnant women, fetuses, newborns, children, and the rest of the public under the guise of protecting them from various diseases." You conclude that by doing so, the government is breaching those individuals' "bodily integrity." Similarly, you argue in subsection C (page P-49 of your petition) that "basic American civil rights and tenants (including informed consent, self determination, and personal autonomy) continue to be violated" ... "because misled and coerced parents offer up their children for infection with mercury-laced pharmaceuticals..."

Regardless of the scope of the Due Process Cause of the Constitution and the "basic American civil rights and tenants" on which you rely, the facts, even as you allege them, do not amount to the government violating anyone's rights. For example, *In re Cincinnati Radiation Litigation* involved doctors who were alleged to have subjected indigent cancer patients to increasing levels of radiation to determine what levels that the human body can withstand, even though the doctors knew that the radiation had no therapeutic value to patients. Allegedly the doctors never informed the patients about any

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of those facts, but instead told them that the radiation was to treat their cancer. In contrast, here you are not denying that the vaccines and other products have prophylactic or therapeutic value to those who take them. Nor have you provided any evidence to claim that FDA officials have been hired to conduct “uncontrolled involuntary experiments” on people. Nor do you claim that FDA has hidden any facts from those who will use thimerosal-containing products. You simply disagree with the conclusions that FDA draws from those facts. As explained above, however, FDA’s conclusions are based on sound scientific principles.

Moreover, as explained extensively above, studies and other evidence support FDA’s determination that vaccines and other FDA-approved products containing thimerosal are safe. The evidence on which your petition relies either does not support your requests, or is too flawed to be considered valid scientific evidence. Therefore, FDA has no grounds to revoke the licenses and withdraw the approvals of thimerosal-containing products, or to take any of the other actions that you seek. Consequently, even if constitutional or other “civil rights” were considered to exist in this context, declining to take any action against those products does not violate anyone’s constitutional or other rights.

#### IV. AGENCY CONCLUSIONS

For the reasons discussed above, the studies and other documents on which you rely do not support your argument that FDA should take action against biologics and other drugs that contain thimerosal. Only a small number of licensed and approved products still contain thimerosal, and the available evidence supports FDA’s conclusion that all currently licensed vaccines and other pharmaceutical drug products containing thimerosal are safe.

For these reasons, we deny your petition in its entirety.

Sincerely,

Jeffrey Shuren, M.D., J.D.  
Assistant Commissioner for Policy

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#### c. Petitioners’ Approach to the FDA’s Assertions

The petitioners, *having updated their requests to reflect the current, 2007, understanding of:*

- ❖ The flaws in the EPA “guideline” for daily mercury intake that, *even for “methylmercury in fish,”* have rendered it a standard with no, or *less than no*, safety margin in humans, and

- ❖ The toxicological science and the clinical and toxicological evidence establishing that injecting Thimerosal (49.55% mercury by weight) into pregnant women and young children mercury poisons these rapidly developing children to varying degrees, including some who, *for whatever reasons*, are mercury poisoned to the extent that they exhibit a clinical level of mercury poisoning,<sup>222</sup>

have used our understanding to address the statements made in the FDA's "SEP 26 2006" letter.

In addition, *at levels below that induced in inoculated children*, the toxic effects of Thimerosal on the immune system have been further elucidated to the point that it is clear that Thimerosal has been proven to be a powerful immune-system dysregulator in humans.<sup>223</sup>

Having reviewed these Agency defenses and justifications, the petitioners will, *on the pages that follow*, now assess each FDA position from the point of view of the scientific and legal issues set forth in this citizen petition.

[Note: To aid any reader in following these discussions, when the letter's printed statements are quoted, they are quoted in an *italicized "Times New Roman"* font followed by the petitioners remarks in indented text written in "News Gothic MT"; quotes from reference articles and documents will be presented in "Arial"; and federal laws, statutes and court decisions will be quoted in a "Lydian" font.]

#### **d. Petitioners' Assessment of Government's Defenses for Allowing Mercury In Drugs**

*"We first address the underlying basis for all the actions you request: your contention that all licensed and approved products containing thimerosal are unsafe. The first part of our discussion*

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<sup>222</sup> a. Nataf R, et al. Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. *Toxicol Appl Pharmacol* 2006; **214**: 99-108.

b. Geier DA, Geier MR. A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure *Neurotox Res* 2006; **10**: 57-64.

<sup>223</sup> a. 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; **214**: 43-54.

b. Havarinasab S, Lambertsson L, Qvarnstrom J, et al. Dose-response study of thimerosal-induced murine systemic autoimmunity. *Toxicol Appl Pharmacol* 2004; **194**: 169-179.

c. Havarinasab S, Haggqvist B, Bjorn E, et al. Immunosuppressive and autoimmune effects of thimerosal in mice. *Toxicol Appl Pharmacol* 2005; **204**: 109-121.

d. Agrawal A, Kaushal P, Agrawal S, et al. Thimerosal induces TH2 responses via influencing cytokine secretion by human dendritic cells. *J Leukoc Biol* 2007; **81**: 474-482.

e. Goth SR, Chu RA, et al. Uncoupling of ATP-mediated calcium signaling and dysregulated interleukine-6 secretion in dendritic cells by nanomolar Thimerosal. *Environ Health Perspect* 2006; **114**: 1083-1091.

*explains how FDA came to the conclusion that those licensed and approved products are safe. The second part explains why the studies on which you rely do not support your contention.”*

First, the petitioners find the “*contention that all licensed and approved products containing thimerosal are unsafe*” misstates the underlying basis for all the actions 2004P-0349/CP1 requested.

Factually, the underlying bases for all of the actions requested are:

1. The FDA’s licensing and/or approval of preserved drug products that the manufacturers have not been proven to be safe to the extent required by **21 CFR § 610.15(a)** – “preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient,” and
2. The failure of the Secretary of Health and Human Services, through the Agencies who report to him, to comply with the clear mandate to safen “childhood” vaccines by reducing the risks of adverse reactions to vaccines through any and all means within the Secretary’s authorities, a clear “shall” requirement set forth in **42 U.S.C. Sec. 300aa-27(a)(2)** – “General rule In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall - (1) ..., (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines, ...”

That lack of “proof of safety” is an underlying basis for 2004P-0349/CP1, is clearly stated in the opening statement of 2004P-0349/CP1 (with underlining added for emphasis):

#### **“I. Actions Requested**

Petitioners request:

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

This “proof of safety” basis is further established in the next point raised on page “P-1” of 2004P-0349/CP1, which states (with dashed underlining for emphasis):

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

subjects. [Note: We make this request because, as all parties (federal government, industry, academia, and the public) know, " all such current products lack the appropriate safety studies. ...]"]

Furthermore, the FDA's "(t)he first part of our discussion explains how FDA came to the conclusion that those licensed and approved products are safe" ignores the reality that under *Berkovitz v. U.S.*,<sup>224</sup> a unanimous 1988 Supreme Court case that recognized the FDA's administrative discretion is limited by any clear policy, legal, or statutory requirement that must be met, a drug must meet all safety requirements before the FDA, or any governmental Agency, can use its discretion to determine "safety" by weighing the drug's potential benefits against its known risks, as the FDA here claims the Agency is allowed to do for biological drug products using the definition of "safety" set forth in **21 CFR § 600.3(u)**, which the FDA asserts, *later in this letter, is implicitly* applicable to all drugs.

Since: a) **21 CFR § 610.15(a)** clearly sets a minimum "proof of safety" requirement for "preservatives" in biological products which implicitly applies to all preserved drug products (just as the FDA held for **21 CFR § 600.3(u)**), and b), *as has been repeatedly admitted by the FDA*, the studies required to prove that preservative levels of Thimerosal or other mercury-based compounds, *taken as being between "0.001% and 0.01%"* (based on the FDA-approved labeling on licensed and approved drugs where Thimerosal is declared as a preservative) are "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" have not been conducted

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<sup>224</sup> *Kevan Berkovitz, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, v. United States* No. 87-498. Argued April 19, 1988. Decided June 13, 1988. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

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

Finally, though the FDA states, “*The second part explains why the studies on which you rely do not support your contention,*” petitioners find that, *since the Agency provides no evidence to substantiate most of its explanations and, in some cases, failed to even accurately portray the studies the Agency purports to be explaining,* the FDA has failed to explain why the cited supportive studies upon which the 2004P-0349/CP1 relied do not support the evidence-based “contentions” raised in that citizen petition.

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

First, since the FDA fails to:

- Present or cite substantive science to support its views on safety in most cases,
- Mention, much less address, the clear requirement minimums for preservatives (see **21 CFR 610.15(a)**) that must be met before any preserved drug can be licensed or approved.
- Mention, much less address, the statutory “Mandate for safer childhood vaccines” (**42**

**U.S.C. Sec. 300aa-27)** that requires the Secretary to use all authorities to “reduce the risks of adverse reactions to vaccines,”

the petitioners find that, *contrary to the FDA’s assertions*, the Agency failed to address the legal arguments presented in 2004P-0349/CP1.

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

- Establish that “*none of the legal actions or remedies*” sought “*are warranted*,” or
- Address the substantive issues raised in 2004P-0349/CP1.

Finally, with respect to the FDA’s “*We then explain why your claims that the government has violated people’s rights lack merit and do not support your petition*,” the petitioners find that the Agency’s explanations:

1. Do not address the reality that the government has ***knowingly***<sup>225</sup>:

- Failed to fully disclose to the recipients or their parents or legal guardians all the risks and the true risk incidences associated with each vaccine (e.g., recent smallpox vaccine case where the government’s claimed risk of death was 1 in 1,000,000 and, for serious harm, about 1 in 100,000, but, as *about 38,000 first providers found out*, the real rates were closer to 1 in 10,000 for deaths and 1 in 100 for severe adverse reaction),
- Inaccurately tracked the adverse reactions to vaccines by failing to provide monetary and other sanctions for the failure of a healthcare provider to report an adverse event (e.g., even the government admits that < 10% of adverse reactions to vaccines are reported to the government and entered into VAERS, the “Vaccine Adverse Events Reporting System” database),

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<sup>225</sup> 21 U.S.C. Sec. 321(bb), “The term ‘knowingly’ or ‘knew’ means that a person, with respect to information -  
(1) has actual knowledge of the information, or  
(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.”

- Not assessed the long-term (beyond 6 months) risks associated with each vaccine even when there is evidence that the adverse reactions for a given vaccine may occur years after inoculation (e.g., the “causal relationship between the haemophilus vaccine and the development of insulin dependent diabetes ... 3 – 4 years after four doses of Hib”<sup>226</sup>),
  - Understated the risks for death and serious injury from the each vaccine (e.g., Varivax®)
  - Inflated the effectiveness of vaccines (e.g., Prevnar®),
  - Failed to *fully* disclose the limitations on vaccines that do not cover all strains of the organism for which “protection” is claimed (e.g., the vaccines for Neisseria meningitidis that provide no protection for the strain that causes about 50% of the cases of disease, but the government permits the manufacturers to misrepresent those vaccines as protecting those vaccinated from contracting meningitis), and
  - Supported the continuing use of vaccines that, *based on government data*, are not effective (e.g., the current human influenza vaccines),
2. Are, therefore, defective on their face, and
  3. Have not established that the “*rights violation*” claims “*lack merit and do not support*” the views set forth in 2004P-0349/CP1.

“Here is an outline of our response:

I. *LICENSED AND APPROVED PRODUCTS ARE SAFE*

F. *Exposure to Mercury through Vaccines is Minimal*

1. *Thimerosal in routinely recommended pediatric vaccines has been removed or reduced.*
2. *Adult exposure to thimerosal through vaccines has been reduced.*

G. *Exposure to Mercury through other Biologics and Drugs is Minimal*

<sup>226</sup> <http://www.vaccines.net/newpage112.htm>

1. *Most plasma derivative products are thimerosal-free; the few snake and spider antivenoms that contain thimerosal create minimal exposure.*
  2. *Exposure to mercury through phenylmercuric acetate and thimerosal in nasal and ophthalmic drug products is minimal.*
- C. *The Few Products that Still Contain Thimerosal are Safe*
4. *To be safe means that the benefits outweigh the risks.*
  5. *For the vaccines that still contain thimerosal, the evidence favors rejecting your allegations about risks, and the benefits are lifesaving and well-established.*
  6. *For the drug products that still contain phenylmercuric acetate or thimerosal, the amounts of mercury are at levels well below what any evidence suggests could pose significant risks to human health.*

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

- A. *The Cell Culture Studies Cited do not Demonstrate Harm in the Human Body*
- B. *The Argument that Thimerosal-Containing Products Harm a "Susceptible Population" of Humans is not Supported by the Evidence*
1. *The susceptible population annual studies cited do not prove, or even conclude themselves, that a significant risk exists for susceptible populations among humans.*
  2. *The references cited that report an increase in the autism rate do not link any increase to vaccines, nor support petitioners' argument.*
  3. *The mercury excretion studies in humans do not support petitioners' argument that thimerosal in vaccines causes autism.*
- C. *Arguments that Thimerosal in the Current Amounts is Insufficient to Quality as a Preservative or an Adjuvant are Flawed; Thimerosal does Meet the United States Pharmacopeia Standard for a Preservative where it is being used as One, and Thimerosal is not being used as an Adjuvant*
- D. *The Cited Animal and Human Studies on Thimerosal's Longevity in the Body do not Study the Consequences of that Exposure.*
- E. *The Studies Cited that Recommend Eliminating all Thimerosal from all Products do not Support those Recommendations with Valid Science.*
- F. *The Methyl Mercury Studies Cited are Inconclusive and Inapplicable to Human Vaccines*
- G. *The Ashwood, et al, Mcginnis, and Megson Studies Cited, which Hypothesize that Thimerosal Causes Gastrointestinal Illness, Vitamin A Depletion, and other Problems, Lack Evidence to Support their Theories*

## III. PETITIONERS' LEGAL ARGUMENTS LACK MERIT

- A. *The Actions and Legal Remedies Requested are Unwarranted on Scientific Grounds*
- B. *The Constitutional and Civil Rights Claims do not Articulate any Grounds upon which FDA Should or Could Grant the Petition*

## IV. AGENCY CONCLUSIONS"

The current petitioners first agree that the outline the FDA provided accurately delineates the Agency's response.

***“DISCUSSION***

***I. LICENSED AND APPROVED PRODUCTS ARE SAFE***

***A. Exposure to Mercury through Vaccines is Minimal***

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

With respect to the claim implicit in: “*A. Exposure to Mercury through Vaccines is Minimal,”* the petitioners find that, since:

- a. “*Minimal*” is defined by Webster as “of or pertaining to a minimum; smallest or least possible; as a *minimal* fraction” and
- b. *As the FDA has repeatedly admitted, there is no minimum limit, for added mercury compounds, below which the mercury in drugs has been proven not to harm any human or animal,*

the FDA's implicit claim here is, *at best*, an unsubstantiated belief that the petitioners must reject because, *by binding regulation*<sup>227</sup>, those manufacturers using Thimerosal or other mercury-based compound as a preservative are required to have: **a)** conducted toxicity studies that establish the “preservative used” is “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient” and **b)** submitted those studies to the FDA before, *after November 20, 1973,*<sup>228</sup> the FDA could lawfully:

- a. License, or approve new drug products, or

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<sup>Let-1</sup> <http://www.fda.gov/ola/2002/vaccinesautism1210.html>. Statement of Karen Midthun, M.D., Director, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, FDA, U.S. Department of Health & Human Services, before the Committee on Government Reform, US House, December 10, 2002.

<sup>227</sup> 21 CFR § 610.15(a).

<sup>228</sup> 38 FR 32056.

b. Continue to license and approve existing drug products, which are preserved with mercury-based compounds in either case.

Until April 13, 1988, the FDA could have argued that its administrative discretion allowed the Agency to ignore the clear requirement set forth in **21 C.F.R. § 610.15(a)**.

However, shortly after April 13, 1988, the FDA could no longer legally continue to ignore this clear requirement because the U.S. Supreme Court unanimously ruled<sup>229</sup> [*Berkovitz v. U.S.*<sup>230</sup>] that, when there is a clear requirement established by a federal policy, law, or statute, federal administrators lack the “administrative discretion” to ignore any such binding requirement.

Therefore, The FDA’s failure to adhere to the Supreme Court’s finding that the FDA’s “administrative discretion” is limited and the clear unfulfilled requirement to prove that mercury-based preservatives are “sufficiently nontoxic ...” collectively bar the FDA from making any *unsubstantiated* (by toxicology) “safe level” claim with respect to the exposure to mercury through vaccines.

This is the case because the FDA has no scientifically sound and appropriate toxicology studies that have proven, *as required by law*, what the “sufficiently nontoxic ...” level is for Thimerosal-preserved vaccines.

Thus, *for the reasons stated*, the petitioners must reject your inappropriate use of the word “*Minimal*” in your heading “A.”

With respect to the Agency’s initial statements:

*“The FDA recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has been working with manufacturers for several years to facilitate the development of new vaccines without thimerosal as a*

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<sup>229</sup> 486 U.S. 531, 108 S.Ct. 1954.

<sup>230</sup> *Kevan Berkovitz, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, v. United States No. 87-498*. Argued April 19, 1988. Decided June 13, 1988. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: 486 U.S. 531, 108 S.Ct. 1954.)

*preservative and to remove or reduce the thimerosal content of existing, licensed vaccines,”*

the petitioners note that your rhetoric here is not consistent with the FDA’s actions.

For example, *knowingly* disregarding:

- ❖ The 1987 statutory mandate to improving vaccine safety by reducing the risk of adverse events set forth in **42 U.S.C. § 300aa-27(a)(2)** and
- ❖ The CGMP “sufficiently nontoxic ...” safety requirement *minimum* for safety set forth in **21 C.F.R. § 610.15(a)**,

the Secretary, the CDC, and the FDA have, *since late December of 1987 (when **42 U.S.C. § 300aa-27(a)(2)** became effective)*, participated in:

- a. Adding several Thimerosal-preserved vaccines (e.g., the Thimerosal-preserved Hib, Hep B, and influenza vaccines) to the recommended childhood vaccination schedule (without toxicological proof of “sufficiently nontoxic ...”) and
- b. Including Thimerosal-preserved influenza vaccines in the recommended vaccination schedule for pregnant women (not only without toxicological proof of “sufficiently nontoxic ...” for the recipient but also without the requisite reproductive toxicity studies required for drugs approved to be routinely administered to pregnant women)

for all who would be directly or, *in the cases of the fetuses in pregnant women*, indirectly administered such Thimerosal-preserved vaccines.

The addition of the Thimerosal-preserved influenza vaccines to the recommended vaccination schedule for pregnant women and children 6 months of age to 23 months of age in 2002 and, *in 2006*, effectively extending the vaccination age for children to 59 months of age as well as continually expanding the “risk” groups of children, expanding the age range for two doses in a single year in “risk” groups of children to

6 months to “less than 9 years” in 2007,<sup>231</sup> and expanding the “risk” groups of adults who should be vaccinated *obviously contradicts* the Agency’s “*FDA recognizes and supports the goal of reducing exposure to mercury from all sources*” rhetoric.

This is the case because the FDA and the CDC have, *after a 1999 promise to remove Thimerosal from childhood vaccines as soon as possible*, instead acted to again *significantly* increase the exposure of fetuses and children to mercury since 2002.

Thus, the actions of the CDC and the FDA clearly contradict the Agency’s assertion here.

Moreover, since the critical factors for exposure are susceptibility and the specific dose (dose per weight), the FDA has increased the specific-dose-exposure in fetuses (known to be more susceptible to mercury poisoning than adults) and young children (presumed more susceptible than adults) to the point that, *if the fetus is dosed when it is large enough to survive the mercury poisoning it receives when the fetus’ mother is inoculated with a Thimerosal-preserved influenza vaccine*, the specific dose administered to children today is much more than half the specific dose that children of non-Rh-negative mothers in the late 1990s by age 5 and no less than half of the specific dose that children of most U.S. Rh-negative mothers received by age 5 in the late 1990s.

Because the level of mercury exposure from vaccines is “near zero” in several European countries, we find it implausible that any prudent person would accept your contention that the FDA truly “*supports the goal of reducing exposure to mercury from all sources*” when, *since 2002*, the developing children’s *maximum* level of mercury exposure from vaccines has been increasing.

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<sup>231</sup> <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm>, FIGURE. Algorithms for determining recommended immunization actions for children

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

- Order all manufacturers to stop using any preservative that does not meet the clear requirements of **21 C.F.R. § 610.15(a)** that have been in effect since 1973 because risk of mercury toxicity (poisoning) is an obvious “adverse reaction” risk, and
- Revoke the license of those vaccines and other preserved drug products lacking the requisite minimum proof of nontoxicity,

but, *to date*, has not used that authority.

Thus, we find your “*FDA has been working with manufacturers for several years to facilitate the development of new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines*” rhetoric to be both:

- Unconvincing and
- At odds with the law.

*“Under the FDA Modernization Act (FDA MA) of 1997, FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines. Conducted in 1999, this review found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions.”*

We find that your assertion, “*this review found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions,*” is at odds with the facts given, among other documents, the findings of the “**Mercury in Medicine – Taking Unnecessary Risks**” (May 2003) staff report<sup>232</sup> from the Subcommittee on Human Rights and Wellness, Government Reform Committee of the US House of Representatives, which was published following a three year investigation.

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<sup>232</sup> **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].

This report specifically stated:

“This argument – that the known risks of infectious diseases outweigh a potential risk of neurological damage from exposure to thimerosal in vaccines – is one that has continuously been presented to the Committee by government officials. FDA officials have stressed that any possible risk from thimerosal was theoretical, that no proof of harm existed. However, the Committee, upon a thorough review of the scientific literature and internal documents from government and industry, did find evidence that thimerosal did pose a risk.”<sup>233</sup>

Additionally, among this report’s key findings were:<sup>234</sup>

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

Furthermore, based upon the published results of the 1999 review by Ball et al.,<sup>235</sup> published in 2001, the petitioners find that the FDA did not consider the vaccine-applicable scientific evidence proving that Thimerosal and its ethylmercury breakdown products are toxic in humans, other animals, and tissue culture systems.

Additionally, the Agency did not, and has yet to, produce the statutory clinical or scientifically sound and appropriate toxicological evidence demonstrating Thimerosal or any other mercury compound, as a preservative in vaccines, is “sufficiently non-toxic ...” to all recipients of vaccines or other drug products preserved with such compounds.

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

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<sup>233</sup> *ibid.*, page 5.

<sup>234</sup> *ibid.*, page 7.

<sup>235</sup> Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics*. 2001 May; 107(5): 1147-1154.

With respect to the previous review by the FDA in 1999<sup>236</sup> and the Ball et al. 2001 article, the petitioners also note, *to our dismay*, that neither group placed appropriate emphasis on the need to evaluate the level of harm to the fetus from the administration of Thimerosal-preserved vaccines to pregnant women.

In the FDA's entire response, the FDA supplied no evaluation or commentary to address this indirect route for administering Thimerosal to the fetus (nor, *for that matter*, any other Thimerosal-containing or mercury-containing drug product used during pregnancy).

Historically, this was somewhat of a moot point<sup>237</sup> because the federal government did not *formally* recommend the routine administration of any Thimerosal-containing vaccine to pregnant women until 2002 (even though, the administration of Thimerosal-preserved influenza vaccines to pregnant women was discussed in the October 1999 "Lister-Hill" workshop on "Thimerosal Vaccines").

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

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<sup>236</sup> Center for Disease Control and Prevention. Thimerosal in vaccines: A joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* 1999 July 9; **48**(26): 563-565.

<sup>237</sup> Though not a general population issue until 2002, the issue of Thimerosal-preserved Rho(D) serum products was an issue during pregnancy for Rh-negative women because of the recommendation that all Rh-negative women receive a Rho(D) injection at 28 weeks into their pregnancy as well as at other events (e.g., spotting, amniocentesis, post-partum) that had been effect since the late 1980s.

In this citizen petition, the petitioners have clearly raised the issue of protecting fetuses from exposure to mercury-containing pharmaceutical products (*i.e.* a Thimerosal-containing influenza vaccine, or any other prescription or over-the-counter drug product, which contains Thimerosal, phenylmercuric acetate or nitrate, or other mercury compound as a preservative) but, *given the Agency's lack of response to this issue*, your silence indicates that you and the Secretary of the Department of Health and Human Services, who is accountable for the actions of the responsible officials in the CDC, FDA and NIH, have *knowingly* decided to ignore this important issue.

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

Historically, studies have shown that both inorganic mercury and organic mercury compounds: **a)** are transmitted by breast milk to a developing infant and **b)** may result in neurodevelopmental disorders in children.<sup>238</sup>

Again, until the early 2000s, this was somewhat of a mute point, *with respect to Thimerosal-containing vaccines*, because Thimerosal-containing influenza vaccines were not recommended, *as they are now*, for routine administration to mothers who may be breast-feeding their infants.

However, under the 2006-2007 and 2007-2008 vaccine recommendations, the Advisory Committee on Immunization Practices (ACIP) and the CDC have

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<sup>238</sup> Amin-Zaki L, Majeed MA, Greenwood MR, Elhassani SB, Clarkson TW, Doherty RA. Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. *J Appl Toxicol* 1981; 1: 210-214.

recommended all mothers with young children should be given an influenza vaccine during the "influenza season."

Since: **a)** some of these mothers may be breast-feeding their infants and **b)** most influenza vaccine doses contain 0.01% Thimerosal, this recommendation represents yet another source of unnecessary mercury exposure for nursing infants whose mothers follow the government's recommendation.

The 2004P-0349/CP1 petition clearly raised the issue of protecting infants from exposure to mercury-containing pharmaceutical products (i.e., Thimerosal-containing influenza vaccine, other Thimerosal-containing vaccine, or any other drug containing any other mercury compound as a preservative, including, *but not limited to*, over-the-counter products containing Thimerosal, phenylmercuric acetate or nitrate, or any other mercury compound as a preservative), but the current petitioners find that the FDA's response has *knowingly* sidestepped addressing the key aspects of this issue including the risk of harm to the fetus and the nursing infant from the indirect exposure to mercury from drugs containing Thimerosal or other mercury compounds.

Also, Special Counsel Scott J. Bloch reported (May 2004).<sup>239</sup>

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

Based on all of the preceding, the petitioners must conclude that, *at best*, FDA and FDA-sponsored reviews have been incomplete.

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<sup>239</sup> Special Counsel Scott Bloch's letter to Congress addressed to: "The Honorable Judd Gregg, United States Senate, Chairman, Committee on Health, Education, Labor and Pensions, 428 Dirksen Senate Office Building, Washington, D.C. 20510-6300 and The Honorable Joe Barton, U.S. House of Representatives, Chairman, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515" [OSC File Nos.: DI-04-1399, et al.].

*“However, as a precautionary measure, and because the elimination or reduction of mercury in vaccines was a feasible means of reducing an infant’s total exposure to mercury in a world where other environmental sources are challenging to eliminate, the Public Health Service (including FDA, the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), and the Health Resources and Services Administration) established the goal of removing thimerosal as soon as possible as a preservative from vaccines routinely administered to infants.”*

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

Second we again note that, in spite of a declared goal to “decrease total mercury exposure, chiefly among infants and pregnant woman”<sup>240</sup> the federal government has, since at least 2002, if not before, raised the maximum level of Thimerosal that “infants” may receive by first recommending, “when feasible,” healthy infants 6-months to 23-months of age be vaccinated with influenza vaccines, including those that are Thimerosal preserved, during the “influenza season”<sup>241</sup> as well as recommending pregnant women who are in their second and third trimesters during the “influenza season” be so vaccinated.

Then, in December 2003, the Center for Disease Control and Prevention (CDC) further increased the maximum vaccine-derived mercury-poisoning burden in infants

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<sup>240</sup> Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2002 Apr 12; **51**(RR03): 1-31 (with underlining added for emphasis): “Although no evidence of harm caused by low levels of thimerosal in vaccines has been reported, in 1999, the U.S. Public Health Service and other organizations recommended that efforts be made to reduce the thimerosal content in vaccines to decrease total mercury exposure, chiefly among infants and pregnant woman (45,46). ... <sup>45</sup> CDC. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. *MMWR* 1999;48:996-8. <sup>46</sup> Stratton K, Gable A, McCormick MC, eds. Immunization safety review: thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC: National Academy Press, 2001.

<sup>241</sup> *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. ...”

up to 23 months of age by officially recommending these babies get two doses of vaccine, separated by a month, the first time they are inoculated.<sup>242</sup>

In 2006, the CDC<sup>243</sup> further increased the mercury-poisoning risk by broadening the influenza-inoculation age range to include children 6-months of age to 59-months of age and removed the “second and third trimesters” restriction for pregnant women.

In 2007, the CDC<sup>244</sup> increased the total number of children in the “risk” groups and recommended 2 doses of influenza vaccine be given to these children at least one time in the period from 6 months of age up to 107+ months of age,<sup>245</sup> effectively adding up to 4 more 0.5-mL doses of the Thimerosal-preserved vaccine to those children given Thimerosal-preserved inactivated vaccine inoculations.

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

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

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<sup>242</sup> **Who Should Get the Influenza (Flu) Vaccine: Interim Recommendations, December 2003.** December 16, 2003, as accessed through the CDC “Preventing the Flu” webpage site: **“Who Should Be Vaccinated With the Flu Shot This Season ... • Emphasis should be placed on targeting trivalent inactivated vaccine (flu shot) to persons at high risk for complications from influenza including: all children aged 6-23 months, adults aged > 65 years, pregnant women in their second or third trimester during influenza season, and persons aged > 2 years with underlying chronic conditions. • All children at high risk of complications from influenza, including those aged 6-23 months, who present for vaccination should be vaccinated with a first or second dose, depending on vaccination status. Doses should not be held in reserve to ensure that two doses will be available.”**

<sup>243</sup> [http://www.fda.gov/fdac/features/2006/506\\_influenza.html](http://www.fda.gov/fdac/features/2006/506_influenza.html), **“Who should get vaccinated? Vaccine is available to anyone who wants to reduce his or her chances of getting influenza, with a few exceptions, but the CDC strongly recommends it for the following groups of people:**

- All children 6 months to 59 months of age—a new recommendation for this influenza season
- Women who will be pregnant during the influenza season ...”

<sup>244</sup> <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm>, **“Prevention and Control of Influenza, Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007”**

<sup>245</sup> Personal communication on Friday, 20 July 2007 starting at about 10:20 EDT with Anthony Fiore, MD, Influenza Division, National Center for Immunization and Respiratory Diseases, CDC, 1600 Clifton Road, NE, MS A-20, Atlanta, GA 30333. Telephone: 404-639-2552

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

Based on these facts, the government has *knowingly* failed to honor the “*eliminate from, or reduce Thimerosal in all vaccines*” goal as the FDA claims here.

In addition, it has ignored its original 1999 commitment to remove all Thimerosal-containing childhood vaccines from the market.

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

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

While your responses here attempt to present the facts in a light that focuses on the vaccines from which Thimerosal has been reduced or removed, your admission that the government has permitted the Thimerosal-preserved inactivated influenza to be added to the vaccination schedule for “*children 6 to 59 months of age*” and, in 2007, for some children 6 months to 107+ months (not “≥ 9” years of age) coupled with permitting Thimerosal-preserved vaccines to be given to pregnant women at any time in their pregnancy without any proof of safety to the fetus as well as allowing Thimerosal-preserved vaccines to be given to nursing mothers clearly show that the

Secretary and the FDA are *knowingly*:

- Ignoring the statutes and laws limiting their discretion and,
- *Contrary to the implications of the FDA's statements here*, increasing the effective mercury-poisoning risk to the "child" by starting the mercury-poisoning before the child is born so that the risk of mercury poisoning to infants receiving the maximum mercury exposure under the current vaccination schedule may, *in some cases*, exceed the previous risk for infants born to Rh-positive mothers when these infants received all of the Thimerosal-preserved vaccines according to the late-1990s' recommended childhood inoculation schedules.

The specific dose, and not just the dose, is important because, *for example*, a fetus weighing about half a kilogram may be exposed to 50 micrograms of Thimerosal (about 25 micrograms of mercury) when his or her pregnant mother is given a flu shot for a specific dose of up to 50 micrograms of mercury per kilogram of body mass (50 parts-per-billion [ppb] mercury).

In contrast, *for example*, prior to recommending giving the Thimerosal-preserved inactivated-influenza vaccine to be given to pregnant women in 2002, a 3 kg (6.6 pound) child born in 2001, who received a 0.25-mL dose of an in-date Thimerosal-preserved hepatitis B vaccine at birth, would have received a specific mercury dose of only about 4.2 micrograms of mercury per kg (4.2 ppb).

Thus, *ignoring the potential toxicity differential between the fetus and the newborn*, the example fetus's specific dose would be up to "12 times" the specific dose received by our example newborn child.

Based on the preceding, it is clear to the petitioners that the federal government, *by adding the Thimerosal-preserved inactivated-influenza vaccines to the recommended vaccination schedule for pregnant women without conducting the requisite reproductive*

toxicity studies to establish what the safe level is for the fetus or apparently even considering the increased risk of mercury-poisoning the fetus, has, in spite of the FDA's glib rhetoric, knowingly increased the risk of mercury poisoning of children *in utero* rather than, as their statements imply, reducing the risk of mercury poisoning children with mercury in the vaccines they directly and indirectly (*in utero*) receive.

Thus, the petitioners find that the FDA's rhetoric is a blatant attempt to mislead the reader to think that the mercury-poisoning risk has been reduced by focusing on childhood vaccines from which Thimerosal has been removed or had its level reduced without even mentioning the increased mercury-poisoning of the children *in utero* when the children's mothers are inoculated with a Thimerosal-preserved vaccine while pregnant with them.

*“As to those influenza vaccines. FDA has approved preservative-free formulations (which contain either no, or only trace amounts of, thimerosal) for two licensed inactivated influenza vaccines that are indicated for children. These influenza vaccines continue to be marketed in both the preservative-free and thimerosal-preservative-containing formulations. Sanofi Pasteur's Fluzone is approved for use in children down to 6 months of age. However, during the last influenza season (2005-2006), Sanofi Pasteur had a capacity to manufacture only approximately 7 million doses of thimerosal-preservative free influenza vaccine. For the 2006-2007 influenza season. Sanofi Pasteur has stated that it will produce approximately 11 million doses of thimerosal-preservative-free influenza vaccine. Novartis' Fluvirin is approved for individuals 4 years of age and older. For the 2006-2007 influenza season, Novartis has stated that it will produce approximately 3 million doses of thimerosal-preservative-free influenza vaccine for the U.S. market. In addition, GlaxoSmithKline's (GSK's) Fluarix contains less than 1.25µg/mercury/dose and is approved for individuals 18 years of age and older. Last season GSK produced approximately 8 million doses of Fluarix. The live attenuated influenza vaccine (FluMist, manufactured by MedImmune) contains no thimerosal, and is approved for individuals 5 to 49 years of age. MedImmune estimates that it will distribute approximately 3 million doses of FluMist in the 2006-2007 season. Clinical studies to evaluate the safety and efficacy of FluMist in children less than 5 years of age have recently been completed and are under FDA review.*

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

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

However, since the current established limit for lethal toxicity (apoptosis) of Thimerosal to human neurons is  $< 0.001 \mu\text{g}$  of Thimerosal ( $< 0.0005 \mu\text{g}$  of mercury) per mL of growing neuron mesh ( $< 0.0005 \text{ ppm}$  mercury),<sup>246</sup> the petitioners find, *for example*, that the “reduced Thimerosal” and the “trace Thimerosal” influenza-vaccine doses will, *if administered*, deliver “ $< 2.0 \mu\text{g}$  to  $< 2.5 \mu\text{g}$  of mercury ( $< 4.0$  to  $< 5 \mu\text{g}$  of Thimerosal) to a nominally 4- to 5-kg, 7-month-old children given two doses of influenza vaccine ( $< 0.0004$  to  $0.0006 \text{ ppm}$  mercury).

If nothing else, the petitioners note that, even injecting these “reduced Thimerosal” and the “trace Thimerosal” vaccines, the amount of mercury injected may, *even if you allow a 2-fold dilution at the injection site*, exceed the established proven-human-neuron-poisoning level ( $< 0.0005\text{-ppm}$  mercury) at the injection site by more than a factor of 2,000 and will, *if you presume preferential absorption in the brain and other tissues*, exceed the toxic level observed for developing neurons in the brain in some cases.

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

Thus, *given the your estimates*, there will be no more than 14 million Thimerosal-preservative-free influenza vaccine doses for children  $< 59$  months through 2007.

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<sup>246</sup> Parran DK et al. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. *Tox Sci* 2005; **86**(1): 132-140.

Hence, again, based upon the population numbers reported in your response, there are 20 million infants and children in this age group, many of whom will need two doses each, then, *based on an uptake rate of 40%*, there should be more than 16 million Thimerosal-preservative-free doses.<sup>247</sup>

However, some of these doses will be administered to older children and adults, including, for example, pregnant women and, *based on the previous years' experiences*, a significant percentage of the "preservative free" doses will be unused.

Thus, several million children in the "under 60 months" age group who will, *if inoculated as recommended*, receive up to 6 doses of a Thimerosal-preserved influenza vaccine and up to 125 micrograms of mercury from post-natal influenza vaccine alone (up to 150 micrograms of mercury if their mother was given a flu-shot while pregnant).

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

Thus, based upon the need to vaccinate *"approximately 180 million Americans for whom the vaccine is recommended,"* state laws, and the presumption that: **a)** most all of the 14 million doses of the "no" Thimerosal and "trace" Thimerosal vaccines will be administered to the affected children and **b)** the pregnant women and women with children under six months of age will receive either some of the "no" Thimerosal and "trace" Thimerosal vaccines, if they are under 18 years of age or, if 18 or older, GlaxoSmithKline's Fluarix®, the petitioners find that about 12 million *"children 6 to 59*

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<sup>247</sup> Given the expansion of the recommendations for children in the widened risk groups so that those up to 9 years of age are now recommended to get a flu inoculation, an additional 8 million-plus doses of "no Thimerosal" or, at least, "reduced Thimerosal" influenza vaccine would be needed – for a total of 24 million of such doses approved for children.

*months of age*” will either: a) not receive an influenza vaccine dose or b) be vaccinated with a Thimerosal-preserved vaccine.

Given the “*approximately 180 million Americans for whom the vaccine is recommended*” and subtracting the 24 million “*children 6 to 59 months of age*” and pregnant and other women discussed above, this leaves about 156 million Americans who will receive one of the remaining about 5 million doses of GlaxoSmithKline’s “reduced Thimerosal” Fluarix, or the 3 million doses of MedImmune’s FluMist® (live-virus), or about 90 million Thimerosal-preserved inactivated-influenza vaccine doses for a total of 98 million doses.

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

Since the government is now projecting 120-plus-million doses but less than 14-million “no Thimerosal” and “reduced Thimerosal” doses approved for administration to children under 5, it should be obvious that, *given previous uptakes of less than 100-million doses*, there will be more than enough influenza vaccine doses but there will be shortages of the “no Thimerosal” and “trace Thimerosal” vaccine doses for the young children and pregnant women.

Considering that the Public Health Service (PHS), American Academy of Pediatrics (AAP) and the manufacturers agreed to remove Thimerosal from all childhood vaccines in July 1999,<sup>248</sup> and as of July 2007 (8 years later), a large portion of American children who are recommended to receive influenza vaccine and whose parents or guardians choose to have them inoculated will still be forced to take a “Thimerosal Preserved” inactivated-influenza vaccine as well as, in some cases, some other “Thimerosal Preserved” vaccines in at least some formulations (e.g., tetanus-diphtheria toxoid, Japanese Encephalitis, tetanus-toxoid, meningococcal meningitis), the government’s recommended vaccination policies have *effectively* been designed to continue the unnecessary mercury poisoning of children by Thimerosal by:

- Actually increasing the level of Thimerosal-derived mercury to which some fetuses are exposed (by adding the influenza vaccine to the recommended vaccination schedule for pregnant women),
- Keeping the level of Thimerosal-derived mercury injected into most vaccine-program-complying American children from dropping to the pre-1980s levels (by adding influenza-vaccine inoculation to the vaccination schedule for young children [initially 6-months of age to 23 months of age in 2002 but increased to 6 months to 59 months of age in 2006, and, *in risk groups*, to 107+ months in 2007]),
- Repeatedly failing to mandate that all vaccines, *including the influenza vaccine*, given to pregnant women and young children contain no added Thimerosal and,
- Directly, and through CDC-supported special-interest groups and health officials,

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<sup>248</sup> Notice to Readers: Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* July 09, 1999; **48**(26): 563-565, with underlining added for emphasis, “Nevertheless, because any potential risk is of concern, the Public Health Service (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible.”

thwarting and/or attempting to thwart the efforts of parent groups in the various States and of federal legislators<sup>249</sup> to pass and/or implement legislation that restricts or bans the use of Thimerosal-preserved and/or Thimerosal-containing vaccines for pregnant women and young children.

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

In addition, the petitioners find that the government's actions for the human "flu" vaccines are both scientifically incomprehensible and medically unsupportable since, *based on the government's own statistics*, history has shown us that the inactivated-influenza vaccines are *not* effective<sup>250,251</sup>.

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

Petitioners find that your statement:

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

is, at best, misleading.

Factually, *until the late-1990s*, a Rh-negative pregnant woman receiving a single generic Thimerosal-preserved Rho(D) product injection could add up to 50 to about 75 micrograms of mercury for a total dose of 237.5 to about 262.5 micrograms of mercury from conception until 6 months after birth.

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<sup>249</sup> CDC letter to staff of the members of Congress opposing Sec. 219 of H.R. 3043 (Sec. 219 forbids using federal funds for Thimerosal-containing influenza vaccines for children under 3 years of age in the 2008-2009 flu season) – H.R. 3042 passed by more than 60% of members on 19 July 2007 but language is not currently in Senate version.

<sup>250</sup> 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.

<sup>251</sup> Based in the preceding finding, we now also assert that the FDA should revoke the licensing of all influenza vaccines for those groups where post-approval in-use studies have failed to demonstrate in-use effectiveness.

**[Note:** For women who were given multiple Thimerosal-preserved generic Rho(D) shots during pregnancy, their developing child was exposed to up to an extra 50 to 75 micrograms of mercury for each shot. In addition, since RH-negative mothers receive another Rho(D) shot after giving birth, an additional up to 15 to 75 micrograms of Thimerosal-derived mercury could have been given to the children of these mothers who nursed their children.]

Factually, *beginning in the late 1990s and with increasing urgency in the early 2000s*, pregnant women began to be advised to get a flu shot when the only available shots were Thimerosal-preserved until the 2001-2002 flu season.

Thus, children born to these mothers could have easily received a maximum dose of 212.5 micrograms of Thimerosal-derived mercury or more – significantly more than your *“maximum cumulative exposure to mercury via routine childhood vaccinations during the first 6 months of life was 187.5 micrograms.”*

**[Note:** There are documented cases where the child of an RH-negative mother who had multiple episodes of spotting during pregnancy was exposed to more than 200 micrograms of Thimerosal-derived mercury from Thimerosal-preserved Rho(D) serum products before birth.]

Moreover, we note that, *based on specific toxicity and actual experience*,<sup>252</sup> the mercury-poisoning effects caused by the pre-natal 15- to 75- µg dose of Thimerosal are obviously much more severe than the effects for the same dose given after birth.

*“With the introduction of thimerosal-preserved-free formulations of DTaP, hepatitis B, and Hib, the maximum cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life.”*

Petitioners again find that the FDA’s statement:

*“With the introduction of thimerosal-preserved-free formulations of DTaP, hepatitis B, and Hib, the maximum cumulative exposure from the routinely recommended*

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<sup>252</sup> 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.

*childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life”*

is, at best, misleading.

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

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

Factually, the minimum “*cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life*” and not the “*maximum*” as the FDA incorrectly asserts.

Obviously, as the “*thimerosal-preserved-free formulations of DTaP, hepatitis B, and Hib,*” approved during the early 2000s began to displace their Thimerosal-preserved counterparts, the percentage of infants receiving the maximum mercury dose would have declined along with the incidence rates for adverse mercury-poisoning-related effects, if any.<sup>253</sup>

Since an initial drop in mercury-poisoning-related disorders was observed as the maximum level of Thimerosal dropped, the petitioners find that this initial drop confirms the reality that those disorders are tied to the mercury-poisoning effects of Thimerosal.

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<sup>253</sup> Factually, research studies into the changes in the incidence rates for autism and other neurodevelopmental disorders that are based on symptoms that mercury poisoning is known to elicit found that there was a decline in these during the early 2000s (see, for example, Geier DA, Geier MR. A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. *Neuro Endocrinol Lett.* 2006 Aug; 27(4): 401-413).

[**Note:** The petitioners have also observed that the “rebound” increases seen beginning in 2006 in the California may, *in part*, be attributed to the effect of the recommended influenza shot for pregnant women that was added to their recommended immunizations without the required reproductive toxicity studies to prove the Thimerosal-derived mercury is not toxic to the developing child in utero. This conscious (or unconscious) desire, on the part of the federal government and State health officials, to ensure that there is no precipitous drop in ASD cases may have also motivated the use of a putative “available vaccine” shortage that was used by California health officials to permit the “emergency” use Thimerosal-preserved influenza vaccines for inoculating young children and pregnant women there in the first “six weeks” of the California 2006-2007 flu season and the similar “cost emergency” used to permit the parallel use of Thimerosal-preserved influenza vaccines in Illinois. Without these manufactured emergencies, the use of Thimerosal-preserved influenza vaccines would have been illegal for pregnant women and young children in California and Illinois for the 2006-2007 flu season.]

*“With the addition in 2004 of influenza vaccine to the recommended vaccines, an infant could receive a thimerosal-containing influenza vaccine at 6 and 7 months of age. This would result in a maximum exposure of 28 micrograms during the first 7 months of life via routine childhood vaccinations.”*

First, the petitioners find that the administration of influenza vaccines to children 6-months to 23-months, *when feasible*, was first recommended by the CDC ACIP in 2002<sup>254</sup> – not “in 2004.”

Building on the 2002 recommendation, in December of 2003, *in addition to keeping the influenza vaccine in the list of “the recommended vaccines” for children 6-months to 23-months*, the CDC<sup>255</sup> recommended two doses for these children the first time they were vaccinated, and also added pregnant women in their second and third

<sup>254</sup> 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.

<sup>255</sup> **Who Should Get the Influenza (Flu) Vaccine: Interim Recommendations, December 2003.** December 16, 2003, as accessed through the CDC “Preventing the Flu” webpage site: “Who Should Be Vaccinated With the Flu Shot This Season”

trimesters to the recommended schedule – not as you stated, “... *the addition in 2004 of influenza vaccine to the recommended vaccines.*”

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

In addition, *since vaccine effectiveness studies have found that the influenza vaccine is no more effective than a placebo for children 2 years of age and under,*<sup>256</sup> it appears to the petitioners that the 2002, 2003, 2004, 2006 and 2007 recommendations are deliberate attempts by federal government officials in the CDC to replace some of the mercury removed from the other previously Thimerosal-preserved vaccine formulations with mercury from the Thimerosal-preserved influenza vaccines added to the recommended vaccination schedule.

Moreover, petitioners again find that your statement:

*“This would result in a maximum exposure of 28 micrograms during the first 7 months of life via routine childhood vaccinations,”*

*knowingly* ignores the mercury-dose contribution from exposing some children *in utero* to the mercury in their mother’s Thimerosal-preserved “flu” shot as well as the potential mercury contributions from other drug products that use a mercury compound as a preservative (e.g., nasal sprays, and eye and ear products).

Based on the FDA’s statements, petitioners find that not only have the FDA, the CDC and the NIH failed to properly evaluate the potential *in utero* mercury exposure contribution to the mercury-poisoning of children given “Thimerosal Preserved” influenza vaccines but also the FDA’s statements here have failed to:

- Accurately reflect the CDC’s recommendations’ timeline for dosing children age 6–23 months and pregnant women or, *worse,*

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<sup>256</sup> 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.

- Address the disconnect between the government’s 1999 recognition of the importance of reducing the maximum Thimerosal exposure in infants and pregnant women<sup>257</sup> and their actions, from 2002 to date, that have increased the maximum Thimerosal exposure from its pre-2002 minimum levels while:
  - Ignoring the known greater sensitivity of the fetus to mercury poisoning and the recognized need for reproductive toxicity studies whenever any prescription drug is to be routinely prescribed to pregnant women as well as
  - Disregarding the obvious increased specific toxicity to the developing child that inoculating a pregnant woman with a “Thimerosal Preserved” influenza vaccine presents.

Further, the petitioners find that the FDA’s reported “*maximum exposure of 28 micrograms during the first 7 months of life*” for mercury fails to take into account all pregnant women who receive a Thimerosal-preserved influenza vaccine (which provides up to 25 micrograms of Thimerosal-derived mercury to the developing child when their mothers are inoculated with a Thimerosal-preserved vaccine).

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

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

Next, between age “3” and age “5,” these children may receive 50 micrograms more mercury – for a total dose of up to 125 micrograms of Thimerosal-derived mercury, provided: **a)** the 2006–2007 (current) schedule remains unchanged, **b)** their healthcare provider adheres to the current schedule, **c)** they do not fall into any “risk”

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<sup>257</sup> 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.

group that may prolong their inoculation (prolonged to 107+ months in the CDC's 2007 recommendations<sup>258</sup>), adding 100 more micrograms of mercury) or through the rest of the childhood (for up to 300-325 more micrograms of Thimerosal-derived mercury), and **d)** the children continue to receive all Thimerosal-preserved vaccines.

Additionally, if the government were to increase the cutoff age and continues to allow Thimerosal-preserved influenza vaccines to be administered, these children might continue to get additional 25-microgram doses annually.

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

Thus, including all of the other Thimerosal-containing vaccines that a child may receive, the present recommended schedule potentially can result in the children getting more than 50% of the total mercury dose that the 1999 schedule provided, with a significant prenatal vaccine-mercury exposure that, *except for some babies born to Rh-negative mothers*, was absent in 1999.

Finally, none of the above calculations take into account that mothers with young children are supposed to get an influenza immunization as well, and, *when they get a Thimerosal-preserved influenza vaccine while breast-feeding their infant*, they will also transmit some, *if not most*, of the vaccine-mercury with which they are injected to the infant through their breast milk.

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<sup>258</sup> <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm>,

“This level is significantly below the Environmental Protection Agency (EPA) calculated exposure guideline for methyl mercury of 65 micrograms during the first 6 months of life for a child in the fifth percentile body weight. (See the enclosure for the x table listing the thimerosal content of vaccines routinely recommended for children 6 years of age and younger.)”

First, the petitioners note that it appears that the Agency has *inappropriately* used the EPA’s estimated reference dose (Rfd) for chronic daily ingestion of “methyl mercury” compounds in a fish matrix – 0.1 µg of mercury/per kilogram of body mass/day.

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

1. The mercury compounds in vaccines are injected in basically an isotonic saline matrix – *not* ingested in a protein-complexed fish matrix, and
2. The vaccine doses are bolus exposures – not chronic low-level exposures.<sup>259</sup>

In addition, the EPA’s estimated (Rfd) for chronic daily ingestion of “methyl mercury” compounds in a fish matrix – 0.1 µg of mercury/per kilogram of body mass/day – has been shown to have overestimated the exposure levels<sup>260</sup> on which this RfD is based and to have underestimated<sup>261</sup> the effects of these lower exposures so that the EPA’s guideline has either no, or a negative, safety margin.

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<sup>259</sup> The medical “drug” analogy to your approach to judging risk would be claiming that taking one diuretic pill a day for 180 days would have the same outcome as taking 18 pills in one day every 10 days or 30 pills in one day once a month. Such approaches ignore the reality that the poisonous side effects of a toxic compound are strongly dependent upon its peak concentration. This is the case because the recipient’s “detoxification” capacity is finite. On a more mundane level, your approach essentially equates drinking 1 shot (oz; 28.3 mL) of an intoxicating liquor (e.g., 80-proof whiskey) every day for 180 days to drinking 60 shots (60 oz; 1.7 L) of that liquor in one day every 60 days. Obviously, even you recognize that the outcomes in these two examples will be drastically different just as they are for periodically inoculating a baby with a dose of a Thimerosal-preserved vaccine.

<sup>260</sup> 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. 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]

<sup>261</sup> a. Gilbert SG, Grant-Webster KS. Neurobehavioral effects of developmental methylmercury exposure. *Environmental Health Perspectives* 1995; **103**(Suppl 6): 135-142.  
b. 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.

Second, as the petitioners have noted, the maximum Thimerosal-derived mercury dose at seven months is closer to 53 micrograms of mercury, *or more*, than it is to the Agency's stated "28 micrograms" because the CDC recommends that women who are pregnant during the "influenza season" should be inoculated with an inactivated-influenza vaccine that may, *in most cases*, be Thimerosal-preserved.

Third, the current petitioners note that the FDA's "*maximum exposure*" statement *inappropriately* presumes that there are no other sources of periodic or chronic mercury exposure to the infant – even though the FDA is well aware of the many Thimerosal-preserved eye and ear drops, nasal sprays, and other drugs preserved with Thimerosal or other mercury compounds that may be and are administered to young children.

Since primate studies in baby monkeys<sup>262</sup> have established:

1. The uptake, transport, metabolism and excretion of the injected Thimerosal varied by more than an order of magnitude in the 17 baby monkeys that were in the Thimerosal-treatment arm even though their dosing was *reportedly* adjusted for the differences in each subject's body weight,
2. On average, a significant part of the Thimerosal injected ended up in the monkeys' brains as "inorganic mercury" where its half-life was estimated to be greater than 120 days<sup>263</sup>,

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

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

<sup>262</sup> Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal. *Environ Health Perspect*. 2005 April 21; **113**(4). 36-page draft "pdf" file. [Final article at doi: 10.1289/ehp.7712 (available online at <http://dx.doi.org>.)]

<sup>263</sup> Based on human autopsy studies on accident victims, the half-life ("half-time") for "inorganic mercury" in the brain was found to be about 20 years. [Sugita M. The biological half-time of heavy metals. The existence of a third "slowest" component. *Int Arch Occup Environ Health* 1978; **41**(1): 25-40.]

3. On average, the half-life for the “organic mercury” (where the organic mercury level is determined by measuring the inorganic mercury level and the total mercury level and subtracting the inorganic from the total) in the brain was about 24 days,

the more appropriate approach to grossly estimating the relative incremental risk for mercury toxicity is to: **a)** divide the amount of Thimerosal injected when a large bolus is injected by twice some guideline value (e.g., the EPA’s 0.1 µg of mercury/kg of body mass/day) and **b)** sum the estimated values found to estimate the maximum relative risk of mercury poisoning in those individuals who do *not* efficiently detoxify themselves from mercury (e.g., those individuals who innately produce low glutathione levels).

Using that approach and, *for example*, a fetus weight of 0.5 kg, a 6-months’ weight of 3.6 kg, a 7-months’ weight of 4.0 kg, an 18-months weight of 10 kg, a 30-months’ weight of 18 kg, a 42-months’ weight of 24 kg, and a 54-months’ weight of 30 kg, the corresponding mercury-poisoning “risk” factors are on the order of:

1.  $20.0 \mu\text{g}^{264} / 0.5 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 400$  for the *in utero* exposure,
2.  $12.5 \mu\text{g} / 3.6 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 34.7$  for the 6-months’ exposure,
3.  $12.5 \mu\text{g} / 4.0 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 31.3$  for 7-months’ exposure,
4.  $12.5 \mu\text{g} / 10 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 12.5$  for the 18-months’ exposure,
5.  $12.5 \mu\text{g} / 18 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 6.9$  for the 30-months’ exposure,
6.  $25.0 \mu\text{g} / 24 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 10.4$  for the 42-months’ exposure, and
7.  $25.0 \mu\text{g} / 30 \text{ kg} \times 10 \text{ kg} / \mu\text{g} = 8.3$  for the 54-months’ exposure,

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<sup>264</sup> Though the fetus has been shown to be a “sink” that accumulates mercury, studies in rabbits indicate that only about 80% of the dose accumulates in the developing fetus.

for, *in this example*, a total of 120 µg of vaccine derived mercury from the bolus inoculations with a total maximum relative risk of about 500.

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

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

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

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

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

The petitioners agree with the FDA that: **a)** the Agency's concern has been focused on childhood vaccines, and **b)** the 2004P-0349/CP1 petition and the current citizen petition, as they should, extend "*to vaccines indicated for all ages.*"

However, since the injected mercury in vaccines and other drugs tends to bioaccumulate in the brain, kidneys, heart and other organs; the degree of accumulation over the "normal" levels is highly variable across both organs and individuals; and the bioaccumulated mercury, *in some cases*, has a two-decades long

half-life in the average person, the petitioners cannot agree that the standard recommendations for adults necessarily lead to “*correspondingly lower mercury exposure from vaccines.*”

Because of the two-plus-decades-long half-life for accumulated tissue bound “inorganic mercury” in various organs and the initial dosing, most people entering the “adult” population under the previous recommended vaccination programs starts out with a maximum organic-derived vaccine-mercury exposure of up to about 240 µg.

Those under the current program may get up to about 125 µg of mercury from the Thimerosal-preserved influenza vaccines received by them up to 59-months of age (or, if in a “risk group, up to 250 µg of mercury from the preserved influenza vaccines by age 9).

Then, all may receive up to two 25-µg doses of organic-derived mercury from the multi-dose Menomune® vaccine (50 µg of mercury), plus one to three 25-µg doses of organic-derived mercury from the TT vaccine (25- to 75- µg of organic-derived mercury) and, *when any at-risk group continues to get an annual preserved “flu” vaccine*, up to twelve, 25-µg doses of influenza-derived mercury (300 µg) for a total of up to 550 µg (about 665 µg, if fully vaccinated under the pre-2000 program, or about 675 µg, if in a “risk” group and vaccinated with a Thimerosal-preserved vaccine until 9 years of age) of vaccine-derived mercury.

Moreover, when this hypothetical “mercury-retaining” person continues to get an annual Thimerosal-preserved flu shot and, *every 10 years*, a tetanus booster vaccine, that person will, *by the time this person reaches 68*, have received a maximum additional 50 times 25 µg of mercury from Thimerosal in Thimerosal-preserved influenza vaccine and 125 µg of mercury from the Thimerosal-preserved tetanus vaccine for a total of 1,925 µg (1.9 mg) of vaccine-derived mercury (or, under the

previous program or in a “risk” group in the “current” program, up to about 2,000 µg [2 mg] of mercury).

Presuming our hypothetical 68-year-old weighs 80 kg and is a non-excretor of mercury, the maximum mercury-poisoning risk factor will then be about 1,925 µg of Hg/80 kg x 10 kg/µg = 240.6 times the EPA’s estimated RfD toxicity risk level (or 250 times RfD risk in “previous” case).

Thus, *ignoring other sources of mercury exposure*, the maximum total vaccine-mercury dose will be about 15 times the level in the child at 59 months and the risk factor will be about 200 times the EPA’s RfD for ingested methyl mercury in fish.

Since, *as the petitioners have shown*, the influenza vaccines are ineffective, the petitioners again note that making influenza vaccination an optional practice and banning the inoculation of pregnant women with any Thimerosal-containing vaccine could lower the example-imputed, mercury-poisoning, maximum-early-childhood relative risk to “about 100,” and the example-imputed minimum relative risk for an elderly adult to “< 25.”

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

*Since the vaccine manufacturers have been able to remove Thimerosal for all of these new vaccines and some manufacturers have been able to totally remove Thimerosal from their existing “Thimerosal preserved” and/or “reduced Thimerosal” vaccines, the*

petitioners see no justification in continuing to license any routine Thimerosal-preserved vaccine – other than to mercury-poison those inoculated – especially since the Thimerosal-preserved influenza vaccines have been shown to be ineffective.

Further, unless and until, the appropriate safety studies prove these preserved vaccine formulations are “sufficiently nontoxic ...” as required by **21 C.F.R. § 610.15(a)**, these Thimerosal-preserved vaccines are clearly adulterated drugs under **21 U.S.C. § 351(a)(2)(B)**, leaving the FDA and the Secretary of HHS in the position of, *at a minimum*, condoning the knowing violation of the law by the firms manufacturing these vaccines and, thereby, placing themselves above the law of the land.

In addition, the petitioners find that the FDA’s recent (5 October 2006) licensing of another Thimerosal-preserved inactivated-influenza vaccine without obtaining the requisite proofs of safety required under **21 C.F.R. § 610.15(a)** after being clearly shown that such an action is a violation of the preceding law and against the clear mandates set forth in **42 U.S.C. Sec. 300aa-27(a)(2)** has plainly signaled the blatant and knowing disregard by the Secretary of HHS and his subordinates for the “law of the land” as established by the Supreme Court in 1988 as well as the FDA’s apparent belief that the Agency and, *through the Agency’s refusal to enforce the law*, the vaccine manufacturers, who continue to produce Thimerosal-preserved vaccines and other drug products containing added mercury, are above the laws of the United States.

As such, it seems to the petitioners that these collusive actions with those vaccine manufacturers (who have, *since 1973, knowingly* held themselves above the this law) fall within the strictures established by the criminal RICO (Racketeering, Influencing, and Corrupt Organizations) statutes as set forth in **18 U.S.C.A Sec 1961 et seq.** and, *in light of the recent licensing of another Thimerosal-preserved influenza vaccine*, the petitioners are compelled to request the Justice Department and, *in States having*

applicable State RICO statutes, those States' Attorneys General to initiate and pursue such actions.

*“The goal of reducing mercury exposure from vaccines must be balanced against the goal of having enough vaccine available. If FDA now revoked the licenses for all thimerosal-containing vaccines, many people would be in serious danger from the diseases that those vaccines prevent. That is true even where a thimerosal-free formulation of the vaccine exists because at this time manufacturers simply cannot produce enough of either formulation for all those who should be immunized.”*

Given the ineffectiveness of the current worst offender, the Thimerosal-preserved influenza vaccines; the FDA's and the CDC's recent knowing actions and inactions; and the clear requirements of the law, the petitioners finds your attempts to justify your knowing failure to act (within the law and as the statutes require you to act) unconvincing.

In addition, petitioners find no evidence of the “*serious danger*” of which you speak and note that you have neither submitted such evidence nor cited papers that contain such evidence.

Further, the petitioners note that officials from Aventis, now Sanofi-Aventis, the principal producers of the remaining Thimerosal-preserved vaccines and many of the “trace Thimerosal” vaccines, have *repeatedly* stated that they would be able to provide sufficient “no Thimerosal” vaccines if the federal government were to mandate that such must be provided.

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

For all of the preceding reasons, the petitioners find your attempts to justify your knowing failure to operate within the applicable laws and statutes to be both unjustified and unjustifiable.

We, therefore, again urge you to abandon your violative ways and conform to the clear legal requirements with which you are required to conform, as the U.S. Supreme Court plainly ruled, *in a unanimous decision (Berkovitz v. U.S.)*.

*“As discussed below in sections I.C and II, neither the evidence you submitted with your petition nor the extensive evidence on the safety of thimerosal-containing vaccines that FDA has reviewed over the years supports your contention that those vaccines are unsafe.”*

Since the FDA has failed to address the laws and statutes cited in 2004P-0349/CP1 and, *in most cases*, has failed to provide any scientific evidence to overcome the peer-reviewed published studies and their findings cited in 2004P-0349/CP1, the petitioners are compelled to reject the Agency’s rhetoric here.

Further, petitioners note that your remarks here concerning the FDA-generated *“contention that those vaccines are unsafe”* clearly ignores the fact that one of the actual contentions in 2004P-0349/CP1 is a contention that Agency has not even addressed, namely the contention that these Thimerosal-preserved vaccines have not, *as required by law*, been proven to be safe to the clear requirement *minimum* standard (“sufficiently nontoxic ...”) for the safety of any chemicals used as a preservative in a biological drug product formulation as set forth in **21 C.F.R. § 610.15(a)**.

In addition, the petitioners again note that you have failed to mention, *much less address*, the other main contention in 2004P-0349/CP1, namely that, *under 42 U.S.C. § 300aa-27(a)(2)*, the Secretary, and CDC, FDA and NIH officials, *individually and collectively*, are required to do all you can to reduce adverse reactions in childhood vaccines and, *as your failure to remove all Thimerosal from vaccines (starting in 1987, when that statute became effective, and continuing to today) clearly establishes*, the responsible federal officials have *knowingly* ignored and flouted this statutory requirement for almost two decades after the U.S. Supreme Court clearly held they did *not* have the “discretion” to ignore the requirements of any federal statute.

Therefore, since the responsible federal officials and agencies have neither addressed these underlying concerns nor presented any substantive proofs, or citations thereto, to support the agencies' claims concerning the applicable petition-supportive evidence submitted or referenced in 2004P-0349/CP1, petitioners must reject the unsupported contentions stated here.

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

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

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

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

Since this is the case for "plasma derivative products," petitioners again wonder why Secretary and FDA officials have not taken similar actions to compel the manufacturers of Thimerosal-containing childhood vaccines that contain a level of Thimerosal shown to cause adverse reactions, including mercury poisoning,<sup>265</sup> to

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<sup>265</sup> a. Nataf R, et al. Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. *Toxicol Appl Pharmacol* 2006; **214**: 99-108.  
b. Geier DA, Geier MR. A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure *Neurotox Res* 2006; **10**: 57-64.  
c. Geier DA, Geier MR. "A Case Series of Children with Apparent Mercury Toxic Encephalopathies Manifesting with Clinical Symptoms of Regressive Autistic Disorders Autistic Disorders," *Journal of Toxicology and Environmental Health, Part A* 2007; **70**: 837-851.

switch to “no Thimerosal” formulations to reduce the adverse reactions such are known to cause under the clear statutory mandate to do so as set forth in **42 U.S.C.**

**Sec. 300aa-27(a)(2).**

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

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

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

**“Sec. 263. Preparation of biological products by Service**

- (a) The Service may prepare for its own use any product described in section 262 of this title and any product necessary to carrying out any of the purposes of section 241 of this title.
- (b) The Service may prepare any product described in section 262 of this title for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section.”

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

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

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

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

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

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

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

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

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

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

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

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

Based on the preceding realities, the petitioners must reject the FDA's stated belief-based contention "*that the mercury exposure from such products is minimal.*"

Thus, the petitioners again call on the FDA to prove, or require the manufacturers thereof to prove, *as the law requires*, that: **a)** these mercury-containing drug products are “sufficiently nontoxic ...” as required by **21 C.F.R. Sec. 610.15(a)**, a CGMP requirement *minimum*, and **b)** these drug products are “safe” in the context of the statutory CGMP compliance expectations set forth in **21 U.S.C. § 351(a)(2)(B)**.

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

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

*Safety is relative, rather than absolute. FDA regulations define safety as “the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time” (21 CFR § 600.3(p)).*”

Provided:

- All the short-term and long-term harmful effects are proven, *by the appropriate scientifically sound toxicological studies, to be minimal*, and
- The safety standard *minimums* established for a given component are met, then the petitioners:
  - Have no problem with the FDA’s using the “safety” definition set forth in **21 C.F.R. § 600.3(p)**, but
  - Note that nowhere in this definition do the petitioners find the simplistic “*benefits outweigh the risks*” phraseology the FDA has chosen to use.

Since all the currently licensed general-use vaccines, *except the rabies vaccine*, are intended to be given to healthy persons, then, under **21 C.F.R. § 600.3(p)**, vaccines should be proven safer than those other categories of drugs that are intended to be given to people that are less than healthy – those having a disease or an illness.

Thus, *in plain English*, this definition does not address, or permit, the Agency's "(t)o be safe means that the benefits outweigh the risks" interpretation of a definition that states:

"The word safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time,"

and clearly requires, *for vaccines*, weighing the "relative freedom from harmful effects" against the "condition of the recipient at that time" without regard to the unknown and theoretical "benefits" because:

- a. Some who are inoculated will get no protection, and
- b. *Unless exposed to the disease*, the protection provided by most vaccines remains, *at best*, only theoretical.

Thus, petitioners reject your simplistic "risk versus benefits" assertion because it is clearly at odds with the definition provided here.

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

First, *if this is how the "FDA finds the product safe,"* petitioners find that the FDA's actions are clearly outside the law based on the definition upon which you claim to rely – namely, **21 C.F.R. § 600.3(p)**.

Second, to the extent this statement implicitly asserts that:

- a. The FDA is the sole arbiter of both the "benefit" and the "risk of the side effects," and
- b. The Agency's "administrative discretion" is not limited by policies, laws and statutes that establish clear safety requirement *minimums*,

petitioners find that, *under Berkovitz v. U.S.*, the FDA's position is at odds with the unanimous findings of the US Supreme Court.

Third, as *petitioners have repeatedly asserted and the FDA has failed to address*, the extent of harm of the “*side effects*” must be proven by suitable rigorous toxicological studies, which, as *the FDA has admitted and Congress has reported*,<sup>266</sup> have not been done for Thimerosal (49.55% mercury by weight), or the other mercury-containing compounds used as process sterilants or preservatives in the manufacture of some vaccines and other drug products – the Agency’s silence clearly establishes the FDA has no rigorous proof that plainly establishes the side effects’ harm.

Lacking proof of the level of harm also means that the FDA lacks “proof of safety.”

Lacking “proof of safety,” the FDA cannot make any valid assessment of “safety” under **21 C.F.R. § 600.3(p)**.

Fourth, *given Berkovitz v. U.S.*, **21 C.F.R. § 610.15(a)**, **21 C.F.R. Part 211**, **21 U.S.C. Sec. 351(a)(2)(B)**, and **42 U.S.C. 300aa-27(a)(2)**, *at a minimum*, the FDA has been explicitly required, *since 1973*, to require the manufacturer of any preserved biological drug product to prove that “the preservative used” is “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient” and, *implicitly*, under **21 U.S.C. Sec. 351(a)(2)(B)**, to prove this level of safety for the preservative systems in all preserved drug products.

Yet, *to date*, the manufacturers of preserved biological drug products have failed to prove that Thimerosal or other mercury-containing compound used as a preservative in their drug products have met this clear “safety” requirement minimum.

Fifth, *given Berkovitz v. U.S. and 42 U.S.C. § 300aa-27. Mandate for safer childhood vaccines*, you have been mandated, *since 1987*, under **42 U.S.C. § 300aa-**

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<sup>266</sup> 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.

**27 (a)(2)**, to do all you can within the authorities of the Secretary of HHS “to reduce the risks of adverse reactions to vaccines.”

Because, *in those who are allergic to Thimerosal*, all Thimerosal-containing vaccines, even the “reduced Thimerosal” vaccines, can and do cause adverse reactions and, *in many cases*, serious adverse reactions including anaphylactic shock and death, the Agency and the Secretary should have been: **a) removing** Thimerosal-containing childhood vaccines from the market as fast as you could from January 1988 onward; **b) refusing** to license or approve any “new” vaccine preserved with Thimerosal or other mercury compound after December 22, 1987; and **c)**, *recognizing that this requirement implicitly applies to all drugs because adverse reaction reduction safens all drugs*, banning Thimerosal and other mercury compounds from all other vaccines and drugs.

However, the FDA actions, including: **a)** recently licensing another Thimerosal-preserved human-influenza vaccine (in 2006) and a Thimerosal-preserved avian-influenza vaccine (in 2007) and **b)** failing to require all vaccine manufacturers to reformulate all their childhood (and other vaccines) without any Thimerosal *clearly* indicate that the FDA has *knowingly* failed to comply with this statutory mandate.

Based on all of the preceding, *at a minimum*, the FDA needs to:

- Correct its violative actions with respect to **42 U.S.C. § 300aa-27(a)(2)**,
- Compel the manufacturers to comply with the law and prove what the safe level is for Thimerosal or other mercury compound (used as a preservative or otherwise) in a drug product formulation – the level at which said Thimerosal or other mercury compound in a biological or other drug product formulation is “sufficiently nontoxic ...” at the maximum dose given to all recipients – such that potential recipients will have no risk of severe short-term or long-term adverse

reactions or evidence of mercury poisoning, as explicitly required for biological products in **21 C.F.R. § 610.15(a)**,

- Enforce the “adulterated drug” sanctions for all preserved vaccine lots where the biological drug product manufacturers have failed to comply with **21 C.F.R. § 610.15(a)**,

before the FDA can legally assess the safety of any “mercury-preserved” mercury-compound-containing biological product (or, implicitly, any other mercury-compound-containing drug product) under **21 C.F.R. § 600.3(p)** because of the highly toxic and bioaccumulative nature of organic mercury compounds in humans.

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

Since the U.S. “post use” history for the inactivated-influenza vaccines has clearly established that they are ineffective,<sup>267</sup> it is clear that, under **21 C.F.R. § 600.3(p)**, such vaccines are also not safe for the recipient.

Based on the preceding reality, the Secretary should immediately stop the CDC’s “recommended influenza vaccination programs,” and order the recall and destruction of all lots of the Thimerosal-preserved inactivated-influenza vaccines because they:

- Are not safe under **21 C.F.R. § 600.3(p)** and
- Have not been proven safe to the extent required by **21 C.F.R. § 610.15(a)**.

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<sup>267</sup> a. 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.  
b. Jefferson T. Influenza vaccination: Policy versus evidence. *BMJ (British Medical Journal)* 2006 October 28; 333: 912-915.

*“Applying that relative standard for safety is critical to the public health because virtually every vaccine — and every drug, for that matter — carries the risk of some side effects.”*

Provided the Secretary and the FDA:

- Operate within the limits on administrative discretion imposed by *Berkovitz v. U.S.*,<sup>268</sup>
- Fully comply with all statutes that govern your conduct (including, but *not* limited to, **42 U.S.C. Sec. 300aa-27** and **21 U.S.C. Sec. 351(a)(2)(B)**),
- Require the drug manufacturers to: **a)** comply with the clear mandated minimums set forth in **21 C.F.R. § 610.15(a)**, **21 C.F.R. Parts 210 and 211**, and any other binding regulations, and **b)** *in light of Vioxx*, fully disclose all studies and all reports of adverse effects within 15-days of their receipt,
- Stop relying on the sponsor’s evaluation of the claimed benefit, and
- Conduct an independent assessment of the real benefits and the true costs per person benefited,

the petitioners have no problem accepting the FDA views stated here.

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

*“In applying the regulatory standards, FDA must weigh the risk of a vaccine — indeed, the risk of any drug — against its benefits when determining whether the product is safe.”*

Petitioners cannot agree with you here because, as stated, your views fail to comply with *Berkovitz v. U.S.*

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<sup>268</sup> Kevan *Berkovitz*, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., *Petitioners, v. UNITED STATES*. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549. (Cite as: **486 U.S. 531, 108 S.Ct. 1954.**)

Based on *Berkovitz v. U.S.*, you must first make sure, in order of precedence, that:

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

before you should begin to weigh the known risks of any vaccine against its putative benefits.

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

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

Petitioners must reject the FDA’s assertions here because:

- The FDA has neither presented nor referenced any body of scientifically sound, peer-reviewed and published “evidence” to support your “*the evidence favors*” assertion,
- Since the “*risks*” claims set forth in 2004P-0349/CP1 are supported by a body of scientifically sound, peer-reviewed and published evidence that 2004P-0349/CP1 both quotes and references, the

claims made in 2004P-0349/CP1 are statements of fact and not, as the Agency states, "*allegations*,"

- The FDA has failed to present or reference any body of scientifically sound, peer-reviewed and published "*evidence*" to support its generalization that "*the benefits are lifesaving and well-established*," and
- The 2004P-0349/CP1 document and the current petitioners have presented scientifically sound, peer-reviewed, published evidence that the influenza vaccines are ineffective, which clearly rebuts the validity of the FDA's generalization here.

*"Thimerosal has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines, with no ill effects established other than hypersensitivity and minor local reactions at the site of injection."*

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

In addition, you have neither responded to, nor considered, the evidence directly presented in 2004P-0349/CP1 with regards to the lack of effectiveness of 0.01% Thimerosal as a preservative in vaccines.

For example, the article by Stetler et al.,<sup>269</sup> *which was submitted with, and referenced in, 2004P-0349/CP1 to show that Thimerosal is not an ideal preservative*, is an article authored by researchers from the CDC.

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<sup>269</sup> 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.

Among other things, the Stetler et al. article, titled "**Outbreaks of Group A Streptococcal Abscesses Following Diphtheria-Tetanus Toxoid-Pertussis Vaccination,**" states:

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

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

Additionally, because the FDA failed to accept the clear evidence provided by the study by Stetler et al. that was reported in 2004P-0349/CP1, the petitioners submit the following series of additional historical studies that clearly establish that Thimerosal is not fully effective as a preservative:

1. An anonymous 1943 *JAMA* publication that questioned the use of Thimerosal as a "preservative," concluded:

"In a recent study of protein sulfhydryl groups Hellerman, Chinard and Deitz point out that organometallic compounds of the type R-Hg-X ... form poorly dissociated protein mercaptides by combination of the organic mercurial with proteins and thiol groups. According to Fildes the formation of such mercaptides is the basis for the bacteriostatic action of mercury. Such sulfhydryl groups are present, however, not only in bacteria but in plasma and other proteins. Bacteriostatic

action of such organomercuric compounds in the presence of serum is therefore largely prevented by competition of reactive groups on the serum proteins for the mercury. This presumably is the basis of the 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..."<sup>270</sup>

2. Morton et al. (1948),<sup>271</sup> under a grant from the Council on Pharmacy and Chemistry of the American Medical Association, published an article on the bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci. They reported:

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

3. Engley (1950)<sup>272</sup> of the Biological Department, Chemical Corps, Camp Detrick published an evaluation of mercurial compounds as antiseptics. Engley judged mercurials to be inadequate as antiseptics:

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<sup>270</sup> Anonymous. Mercurials as "preservatives." *J. Am. Med. Assoc.* 1943; 122: 1253.

<sup>271</sup> 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.

<sup>272</sup> Engley FB. Evaluation of mercurial compounds as antiseptics. *Ann. N. Y. Acad. Sci.* 1950; 53:197-206.

“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 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)<sup>273</sup> presented a paper to the 42nd midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago, Illinois. In that paper, Engley explicitly questioned the acceptance of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating:

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

<sup>273</sup> Engley FB. Mercurials as Disinfectants: Evaluation of Mercurial Antimicrobial Action and Comparative Toxicity for Skin Tissue Cells. Chicago, IL: 42<sup>nd</sup> Mid-Year Meeting of the Chemical Specialties Manufacturer's Association (1956).

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

5. Hekkens et al. (1983)<sup>274</sup> undertook an evaluation of the effectiveness of some preservatives in inactivated human vaccines by application of the test described in the **United States Pharmacopoeia (USP) XIX**. These researchers described that five recommended strains as well as three strains isolated from vaccines were used as test strains. These researchers found that vaccines preserved with Thimerosal did not fully meet the requirements for a vaccine preservative according to the criteria established by the **USP XIX**.
6. Lowe and Southern (1994)<sup>275</sup> evaluated the antimicrobial action of various preservatives for vaccines, and reported:

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<sup>274</sup> Hekkens FE, Polak-Vogelzang AA, Kreeftenberg JG. The antimicrobial effectiveness of some preservatives in inactivated human vaccines. *J Biol Stand* 1983; 9:277-285.

<sup>275</sup> Lowe I, Southern J. The antimicrobial activity of phenoxyethanol in vaccines. *Lett Appl Microbiol* 1994; 18: 115-116.

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

Furthermore, the authors stated,

“... low toxicity of phenoxyethanol in children has been reported...”

Hopefully, after reading these published historical reports, the FDA and any reader will agree:

- Thimerosal is not effective “*in preventing bacterial and fungal contamination of vaccines*” and
- There are other less toxic organic compounds, whose metabolites are not *bioaccumulative toxins*, that are suitable for use as biological drug product preservatives.

In addition, the statement:

*“Thimerosal has a long record ... with no ill effects established other than hypersensitivity and minor local reactions at the site of injection,”*

distorts factual reality.

First, petitioners note that, by the FDA’s own admission, Thimerosal does have established adverse reactions – “*hypersensitivity.*”

In addition, at the start of the first day of the October 1999 “Lister Hill” workshop on “Thimerosal in Vaccines”,<sup>276</sup> Dr. Jerome, Klein from the Boston University School of Medicine, stated in his opening remarks:

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<sup>276</sup> 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,

“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.

Moreover, in considering hypersensitivity, it is significant that, *under worst-case conditions*, this type of adverse reaction can manifest as anaphylaxis and lead to the patient’s death.

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

The only evidence purporting to bear on the safety of using Thimerosal as a preservative are reviews by the IOM<sup>Let-3, Let-4</sup> and the CDC (Parker et al.) that this letter reports, which conclude the evidence is not consistent with Thimerosal’s causing autism but do not directly address its safety or the mercury poisoning it may cause.

After actually reviewing the cited studies, the petitioners find that a significant number do provide peer-reviewed scientific epidemiological evidence showing the possibility of an increased risk for neurodevelopmental disorders, including, *in many*, autism, following exposure to Thimerosal-containing vaccines.

*“Nevertheless, some people have raised concerns about the use of thimerosal in vaccines, and in particular about potential adverse effects of the cumulative amount of mercury that might be administered to a child as a result of routine childhood immunization. These concerns were based on increased awareness of a potential for neurotoxicity of mercury, and on the increased number of thimerosal-containing vaccines that were added to the infant immunization schedule in the 1990’s.”*<sup>Let-2</sup>

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and the Centers for Disease Control and Prevention (National Institutes of Health, Lister Hill Auditorium, Bethesda, Maryland)

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

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

*“In 2001, the Institute of Medicine’s Immunization Safety Review Committee issued a report, based on a review of available data, concluding that the evidence was inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder, and speech or language delay.”*

While the FDA’s statement accurately reflects what the IOM addressed in its report and its key findings, petitioners note that this IOM committee failed to address the issue of cumulative sub-acute mercury poisoning and the clinical effects of this cumulative sub-acute mercury poisoning on those repeatedly immunized with Thimerosal-preserved vaccines, *as many were prior to 2000*, because the reduced-Thimerosal vaccines did not start to become available until late in 2000.

Moreover, *because the existing in-date Thimerosal-preserved vaccines were not recalled but allowed to be used*, there was no precipitous decrease in the maximum dose of mercury that children received or could receive.

Finally, this IOM did not consider or address the effects of repeated exposures to other mercury-compound-containing drugs, dietary mercury intakes, and the cumulative effects of all mercury exposures.

*“The Committee stated that the effort to remove thimerosal from vaccines was ‘a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible.’”<sup>Let-3</sup>*

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<sup>Let-3</sup> IOM (Institute of Medicine). Thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC: National Academy Press, 2001, <http://www.nap.edu/catalog/10208.html>.

While the petitioners find that it is laudable that this letter reports this “Committee” statement, the petitioners note that the letter fails to mention that the federal government and the vaccine makers, *by leaving existing Thimerosal-preserved vaccine stocks on the market after the “reduced Thimerosal” vaccines became available, knowingly choose not to “... ‘reduce mercury exposure of infants and children as much as possible.’”*

*“The IOM issued a follow-up report on May 17, 2004, based on the IOM’s extensive review of the epidemiological studies performed after it issued the 2001 report, some of which you also cited in your petition (in endnotes 38.1, 38.2, 38.3, 34, 40.1, 40.2, 40.3 and 40.4).”<sup>Let-4</sup> “The IOM explained its conclusions as follows:*

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

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

Nevertheless, the absence of statistical evidence at a given confidence level of an association in an epidemiological study is not proof of the absence of an association.

Second, the petitioners note that this IOM report:

- Ignored evidence of an association between Thimerosal and other neurodevelopmental disorders reported in the only study that examined a population of children vaccinated according to the U.S. vaccination schedule (*Verstraeten et al., 2003*), and

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

- Failed to address the ever growing body of toxicological evidence that has clearly demonstrated that repeatedly injecting pregnant women, newborns, babies, children and adults with 0.25- to 1- mL doses of vaccine formulations that contain 0.003% to 0.01% Thimerosal (49.55% mercury by weight), effectively about 0.0016% to 0.005% mercury by weight, mercury-poisons all who are injected with these mercury-containing vaccines to some degree.

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

Based on the preceding realities, the petitioners must conclude that the reported “*no association*” findings, found in the epidemiological studies cited, must be completely discounted.

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

Since neither the IOM nor the FDA have provided any substantive data to support the statements made by the IOM, or any references to any other peer-reviewed published studies that have examined any of the studies cited and found similar problems with them, the petitioners must: **a)** conclude that the

unsupported negative comments reported were simply contrived and **b)** reject the characterizations assigned to these reports.

From a design and execution point of view, these studies were found to be better designed and more properly executed than the studies upon which the IOM committee claimed to rely.

Moreover, since the authors of these studies were willing and able to provide the data they used for independent review while, *in general*, the prior authors were either “unable” or “unwilling” to provide the data sets used for independent review, the petitioners find that the studies referenced here should have been accepted and, *contrary to the IOM’s position*, the other epidemiological studies should have been rejected because there was/is no way for all of the data used in them to be independently evaluated to confirm the findings reported.

Moreover, given this lack of independent repeatability, the petitioners who are also researchers, must discount the epidemiological studies upon which the IOM relied because their results are “non-reproducible.”

Until such time as these studies can be independently replicated, such studies must be considered suspect.

In 2006, the petitioners’ long-held and substantial concerns regarding the problematic nature of the epidemiological studies cited by the IOM committee used to reach its conclusions were partially confirmed by an independent NIH review,<sup>277</sup> which, *in part*, stated:

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<sup>277</sup> An 18-page report issued by an Expert Panel to the NIEHS that is titled “Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using Vaccine Safety Datalink and dated on “August 24, 2006,” which was issued as the Appendix to a 5-page October 2006 NIEHS report, which is simply titled “Thimerosal Exposure in Pediatric Vaccines” [[http://www.safeminds.org/pressroom/pres\\_releases/Thimerosal\\_Pediatric\\_Vaccines.pdf/](http://www.safeminds.org/pressroom/pres_releases/Thimerosal_Pediatric_Vaccines.pdf/)].

“The Report of the Expert Panel stated that ‘The panel identified several serious problems that were judged to reduce the usefulness of an ecologic study design using the VSD to address the potential association between thimerosal and the risk of AD/ASD. These included uncertainties in case ascertainment, heterogeneity of business practices within and across managed care organizations (MCOs) and their systematic changes over time, misclassification of exposure status using comparisons of before vs. after removal of thimerosal from most childhood vaccines, and the inability to control for temporal changes in awareness, diagnostic practices and potential confounding factors. In light of the cumulative effect of these limitations, the panel reached consensus that an analysis comparing the rates of AD/ASD in the VSD over the time period before, during and after the removal of thimerosal from most childhood vaccines would be uninformative and potentially misleading.’ The panel recommended that these gaps be addressed prior to any consideration of further studies of autism and thimerosal using the VSD.”

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

*“FDA concludes that the evidence reviewed by the IOM does not support an association between thimerosal-containing vaccines and autism. In particular, the data from Denmark and Sweden, where exposure to thimerosal in vaccines was eliminated in 1992 and where autism rates continued to increase, underscore this finding (Stehr-Green. et al., 2003).”*

Here, the petitioners disagree with the FDA conclusions and again note that the IOM failed to properly consider, *much less address*:

- The body of peer-reviewed toxicological evidence and
- The fundamental issue of the link between the amount of Thimerosal (49.55% mercury by weight) injected and the incidence of the recognized symptoms of clinical mercury poisoning, including those clinical mercury-poisoning symptoms that are used to diagnose: a given autistic spectrum disorder (ASD) (or pervasive developmental disorder [PDD]).<sup>278</sup>

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<sup>278</sup> Appendix A, “Comparison Of: The Characteristics of “Autism” To Those for Mercury Poisoning,” in “Thimerosal Causes Mercury Poisoning I RebuttalToNovella’sViews.pdf” as published on the “Documents” web page of the CoMeD web site: <http://www.mercury-freedrugs.org/>.

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

In addition to being unable to obtain the data they used so that it could be independently evaluated, the petitioners also note this paper failed to report the clear conflicts of interest of its authors.

Based on all of the preceding, petitioners find that your letter's stated conclusions, *which*:

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

are not supported by any sound toxicological science: **a)** of which the petitioners are aware or **b)** that you have provided or cited in this letter.

*"Furthermore, recent data from a study conducted in Quebec, Canada, also found that there is no relationship between the level of exposure to thimerosal in vaccines and autism (Fombonne, et al., 2006)."*<sup>279</sup>

First, the petitioners note that Fombonne has refused repeated written and verbal (telephone message) requests by the **CoMeD** Science Advisor and other qualified

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<sup>279</sup> 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.

independent scientists to provide all the key data upon which this paper is based so that the paper's data can be independently evaluated and other independent researchers can either verify or disprove this paper's reported findings.

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

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

Furthermore, when **CoMeD's** Science Advisor critically evaluated<sup>280</sup> the little data and information that was included in the Fombonne et al. paper cited in the letter, he found that the data provided failed to support the model used or the conclusions reported in said paper.

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

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<sup>280</sup> "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'sCmnts\\_CanadianEpidemioStudy\\_Pediatrics-Full-b.pdf](http://www.mercury-freedrugs.org/docs/060827_PGK'sCmnts_CanadianEpidemioStudy_Pediatrics-Full-b.pdf).

decrease in the incidence rates for total PDD cases in grades “3” through “1” (containing children *nominally* born in 1995 through 1998, who were, *on average*, given significantly lower levels of Thimerosal-containing vaccines).

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

Thus, the apparently valid data points in the Fombonne et al. paper support the petitioners' views and not the views the Agency has represented this paper to support.

*“This conclusion is further supported by an analysis by Parker, et al., 2004 (Ped. 114: p. 793), who conducted a systematic review of published articles that report original data pertinent to the potential association between thimerosal-containing vaccines and attention deficit disorders/neurodevelopmental disorders. The authors concluded that available data did not demonstrate a link between thimerosal-containing vaccines and autism spectrum disorders.”*

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

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

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

Based on these findings, the petitioners conclude that, Parker et al. does not, as the letter claims, actually support the FDA's "conclusion," just as an in-depth review of the published Fombonne et al. paper does not support its "conclusion" regarding the effect of Thimerosal-preserved vaccines on the rates of PDDs observed.

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

Here, petitioners simply find that the issue of the "*widespread, life-saving benefits*" of vaccines is not an issue that is germane to the safety, effectiveness, and bodily integrity issues that the petitioners have raised in this citizen petition when it has addressed "safety" issues concerning those vaccines that contain the added mercury compound Thimerosal.

*"As discussed above, FDA must weigh theoretical risks against the known benefits of vaccines that would be greatly reduced if FDA were to revoke the licenses for all thimerosal-containing vaccines."*

Again, the FDA's statement ignores the Agency's non-dischargeable higher duties:

- The explicit mandate to do whatever the Secretary of HHS has the authority to do to reduce the risk of adverse reactions in childhood vaccines (as per **42 U.S.C. Sec. 300aa-27(a)(2)**) as well as your *implicit* mandate to, *at a minimum*, take similar actions for all vaccines and other biological drug products.
- The explicit legal responsibility to ensure that the FDA only license vaccines that have met all regulatory requirements including the requirement to prove that the preservative used is:

*"sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient"* (21 CFR § 610.15(a).

Regardless of what arguments the FDA uses to justify its *obviously* knowing actions, the petitioners find that the Secretary of HHS and the FDA officials have failed to: a) comply with the applicable, laws and statutes that regulate their legal

conduct and/or **b)** require the firms, which you are supposedly regulating, to be in “substantial compliance” with all clear CGMP requirement minimums before you can legally license or approve, or continue to license or approve, a vaccine or other drug.

Since: **a)** the Supreme Court has unanimously ruled in 1988 in *Berkovitz v. U.S.* that governmental officials have no administrative discretion to knowingly allow a drug manufacturer not to comply with a clear regulation, and **b)** FDA officials have repeatedly testified that the manufacturers have not conducted the required toxicological studies to establish that the preservative level of Thimerosal administered, or, for that matter, any lower level is “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient,” the FDA’s current actions have the Agency:

- Denying the 2004P-0349 petition without addressing the clear underlying legal issues raised in 2004P-0349 citizen petition,
- Continuing to refuse to compel the vaccine makers to conduct the requisite toxicology studies required for them to comply with the CGMP “sufficiently nontoxic ...” minimum set forth in **21 CFR § 610.15(a)**,
- Continuing to license new Thimerosal-preserved influenza vaccines (e.g., the October 5, 2006 approval of FluLaval) without having proof of safety that meets the “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient” criterion,
- *While having full access to the thousands of adverse reaction reports for hypersensitivity to Thimerosal including those submitted to CBER in the years prior to the creation of the VAERS database:*
  - Persisting in refusing to prohibit the use of Thimerosal, a highly toxic, teratogenic, mutagenic and immunogenic compound at the sub-part-per-million

level (making it at least two orders of magnitude worse than more familiar teratogens, like Thalidomide), or any other mercury-based compound, in the manufacture of any drug product, and

- Refusing to reduce the risk of adverse reactions in childhood vaccinations by requiring all vaccine makers to remove Thimerosal from all childhood vaccines and, thereby, comply with **42 U.S.C. Sec. 300aa-27(a)(2)**,

and

- Continuing to condone the unnecessary mercury poisoning of all fetuses, newborns, babies, children, adolescents, adults and the elderly by the Thimerosal-containing drugs, including vaccines, administered to them or, in the case of the fetuses, their pregnant mothers.

Given the preceding substantiated realities, the petitioners find that the Secretary of HHS and FDA officials are apparently *knowingly* holding yourselves to be above the law and, *hopefully*, the court will: **a)** recognize your actions are needlessly endangering the health of the public and unjustly denying the right of informed consent and **b)** immediately take the appropriate corrective actions when these actions are brought to the court's attention.

*“As to the influenza vaccine, for example, recent analyses estimate an average of 36,000 annual deaths from influenza during the 1990s and an average number of hospitalizations between 114,000 and 200,000, with rates highest among those under 23 months of age and those over 65 years of age.”*<sup>Let-5</sup>

First, petitioners find that these “*recent analyses*” are at odds with the published values reported in a 2006 article<sup>281</sup> covering the period from 1979 to 2000.

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

<sup>281</sup> 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.

Rather than discuss your “estimated” (as your “recent analyses estimate” admits) data, petitioners are including the data table containing the published historical data that were used to assess the “effectiveness” of the influenza vaccine in this response as **Petitioners’ Table 1**.

**Petitioners’ Table 1. A summary of the raw data employed for analysis in Geier et al. (2006)**

Year	Estimated United States Population <sup>1</sup>	Total Net Number of Influenza Vaccine Doses Distributed <sup>2</sup>	Influenza Vaccine Percent Population Coverage [IVPPC]	“Influenza” Death Rate <sup>3</sup> (per 100,000 people) [Total Number]	Influenza Case Rate <sup>3</sup> (per 100 people) [Total Number]	Influenza First-Listed Hospital Discharge Rate <sup>3</sup> (per 10,000 people) [Total Number]
1979 <sup>4</sup>	225,055,487	18,270,794	8.1	0.3 [604]	-	-
1980	227,224,681	12,425,890	5.5	-	-	-
1981	229,465,714	19,829,170	8.6	1.3 [3,006]	-	-
1982	231,664,458	16,959,690	7.3	-	33 [74,925,000]	-
1983	233,791,994	17,877,970	7.6	0.6 [1,431]	38 [87,299,000]	-
1984	235,824,902	19,179,060	8.1	-	45 [103,440,000]	-
1985	237,923,795	20,700,761	8.7	0.9 [2,054]	40 [94,409,000]	-
1990	249,464,396	27,076,206	11	-	43 [106,807,000]	1.8 [44,000]
1991	252,153,092	32,809,662	13	0.4 [1,137]	52 [129,583,000]	1.0 [26,000]
1992	255,029,699	40,352,367	16	-	43 [107,309,000]	0.5 [13,000]
1993	257,782,608	42,980,814	17	0.4 [1,044]	52 [132,633,000]	1 [25,000]
1994	260,327,021	60,084,728	23	-	35 [90,447,000]	1.2 [31,000]
1995	262,803,276	36,512,538	14	0.2 [606]	41 [108,009,000]	0.7 [19,000]
1996	265,228,572	38,915,520	15	0.3 [745]	36 [95,049,000]	0.8 [21,000]
1997	267,783,607	40,996,883	15	0.3 [720]	-	0.7 [19,000]
1998	270,248,003	48,080,122	18	0.6 [1,724]	-	1.3 [34,000]
1999 <sup>5</sup>	272,690,813	60,468,427	22	0.6 [1,665]	-	1.4 [37,000]
2000	281,421,906	65,582,650	23	0.6 [1,765]	-	1.4 [39,000]
			Mean ± std	0.5 ± 0.3 [1,269 ± 786]	38 ± 13 [94 ± 3.4 million]	1 ± 0.5 [25,667 ± 12,323]

<sup>1</sup> Data obtained from the United States’ Census Bureau

<sup>2</sup> Data obtained from the Biologic Surveillance Summaries of the Centers for Disease Control and Prevention

<sup>3</sup> Data obtained from the National Center for Health Statistics

<sup>4</sup> Estimates for 1979 through 1998 use International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9) coding

<sup>5</sup> Estimates for 1999 through 2000 use International Classification of Disease, 10<sup>th</sup> Revision (ICD-10) coding

Based on the government's own historical data for the years reported (see: **Petitioners' Table 1**), Geier et al. found that the influenza vaccines are not effective in either protecting those inoculated from contracting influenza or in stopping the spread of influenza.

Lest the FDA officials or the reader think that these findings are "new," the petitioners would suggest that you read the other peer-reviewed published articles referenced by the Geier et al.

*"During the 2003-2004 influenza season, several states had reported by December 2003 severe complications and deaths related to influenza in children (MMWR 12/19/03, 52(49)1197-1202), Since some of these deaths were in children under 23 months of age, it is clear that there is an actual risk of preventable disease causing death as compared to the theoretical risk of vaccine causing autism."*

First, while the petitioners agree that there are "*severe complications and deaths related to influenza*" in a few children each year (see **Petitioners' Table 2** on the following page), we note that the letter *correctly* said these were deaths "*related to influenza*" and not influenza deaths *per se*.

Based on history, *on average*, we estimate that less than 18 (< 9 – < 31) "*children under 23 months of age*" expire each year from medical conditions that are listed as "influenza related" deaths.

Since about 4 million children are born each year, these deaths translate to an influenza-related mortality rate of about 2 deaths per million children.

While it is sad that any child should die, it is clear that recommending all receive a vaccine for a disease with this mortality rate results in an economically flawed situation, even if you presume, *contrary to factual reality*, that the influenza vaccines were effective.

Factually, the cost per death prevented, the cost per death prevented, *presuming 2*

doses of vaccine at 6 months and 7 months at \$ 25.00 per dose, 1 dose at about 18 months at a cost of \$ 25.00 per dose, and full vaccination, would be on the order of \$ 15 million dollars per death prevented even if, *contrary to the facts*, these influenza vaccines were effective in children under 2 years of age.

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

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

<sup>1</sup> Data obtained from the National Center for Health Statistics

<sup>2</sup> Mean-based death rate for children aged "0"-14 of about 0.5 deaths per million children

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

More significantly, as previously stated, published research<sup>282,283</sup> has shown that the current influenza vaccines are not effective in preventing young children from contracting influenza.

<sup>282</sup> 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.

<sup>283</sup> Maeda T, Shintani Y, Nakano K, Terashima K, Yamada Y. Failure of inactivated influenza A vaccine to protect healthy children aged 6-24 months. *Pediatr Int* 2004; **46**: 122-125.

Specifically, Jefferson et al., the first paper referenced, found that, *for children two years of age and under*, influenza vaccination was no better than a placebo injection in preventing a healthy child from getting influenza.

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

Based on the preceding findings (that the influenza vaccines are not effective for children under 2 years of age as well as for the American public in general), petitioners hope that the Secretary of HHS will halt this program on this basis alone.

Further, with respect to the letter's assertion of a "*theoretical risk of vaccine causing autism,*" which misstates the causal risk as "*vaccine*" when the petitioners have shown that that one risk is clearly the "*Thimerosal*"-derived mercury in the vaccine, petitioners note that you have failed to present toxicological studies that have proven that this risk is "*theoretical*" and, *contrary to your assertion*, petitioners' review of the valid epidemiological data published by Fombonne et al.<sup>284</sup> has clearly shown there is/was some significant correlation between the maximum level of Thimerosal exposure from vaccines and the number of PDD cases reported.

Furthermore, petitioners note that 2004P-0349/CP1 presented ample evidence that Thimerosal causes mercury poisoning in human tissues at levels more than 5,000 times lower than the nominal 50-ppm (0.005%) level of mercury in most Thimerosal-preserved vaccines.

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<sup>284</sup> Fombonne E, Zakarian R, Bennett A, et al. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. *Pediatrics* 2006; 118: e139-e150.

In addition, the recent paper by Parran et al.<sup>285</sup> has extended that toxic differential to more than 100,000 times lower than the vaccine level when those researchers were able to confirm neuron cell death (apoptosis) in developing human neuron meshes from Thimerosal exposures below 0.001 ppm (< 1 part-per-billion; 0.0000001%) – at mercury levels below 0.0005 ppm (<0.5 parts per billion).

Additionally, a 2005 paper by Al-Saleh et al.<sup>286</sup> established that even some of the inorganic mercury applied topically at low levels (< 1 ppm) could accumulate in and cause damage to the brain.

Based on all of the preceding, petitioners must reject this letter's: "2. For the vaccines that still contain thimerosal, the evidence favors rejecting your allegations about risks, and the benefits are lifesaving and well-established" because it is not supported by the scientific information the petitioners have provided in our petition, including this review, or, *for that matter*, by the valid epidemiological data from the recent epidemiological study by Fombonne et al., a paper cited in your letter.

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

Since lethal toxicity for Thimerosal has been established at levels below 0.0000001% (< 0.001 ppm; < 1 ppb) in 2005,<sup>287</sup> we find that your statement conflicts with the current state of knowledge for Thimerosal in drug products.

In addition, since 2004P-0349/CP1 substantiated lethal toxicity to human skin and notochord tissues at Thimerosal levels below 0.0002% (< 0.02 ppm; <20 ppb),

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<sup>285</sup> Parran DK et al. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. *Tox Sci* 2005; **86**(1): 132-140.

<sup>286</sup> Al-Saleh I, El-Doush I, Shinwari N, Al-Baradei R. Does low mercury containing skin-lightening cream (Fair & Lovely) affect the kidney, liver, and brain of female mice? *Cutaneous & Ocular Tox* 2005; **24**: 11-29.

<sup>287</sup> Parran DK et al. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. *Tox Sci* 2005; **86**(1): 132-140.

the petitioners find that the letter's statement here is at clearly odds with reality for Thimerosal in drug products, including vaccines.

For inorganic mercury, petitioners note that the 2004P-0349/CP1 found and also reported developing-neural-cell-mesh toxicity from inorganic mercury ( $\text{Hg}^{2+}$ ) at levels below 0.0002% (< 0.02 ppm; <20 ppb).

Based on these findings, petitioners conclude that this letter's: "3. *For the drug products that still contain phenylmercuric acetate or thimerosal, the amounts of mercury are at levels well below what any evidence suggests could pose significant risks to human health,*" is not supported by the scientific evidence.

"a. *PMA in nasal and ophthalmic drug products*

*PMA is an organic (aryl) form of mercury that is rapidly metabolized to an inorganic form of mercury. PMA is used in nasal sprays and ophthalmic drug products. It has the chemical structure,  $\text{C}_6\text{H}_5\text{HgOOCCH}_3$  (Sax 1984). The rapid conversion of PMA from the organic form to the inorganic form is an important factor in PMA's toxicity profile. Although organic methyl mercury is detectable in experimental animals for weeks after a single injection, phenylmercuric salts are completely converted to the inorganic form within days of dosing (Clarkson 1972). The relatively rapid clearance of inorganic mercury compared to organic methyl mercury helps to render the inorganic forms generally less toxic. Thus, the toxicity caused by PMA is similar to inorganic mercury, with the kidney as the target organ."*

First, reviewing the limited literature on phenylmercuric acetate (PMA), petitioners find that the FDA's statements here have failed to present an accurate picture of PMA's toxicity.

Moreover, no clearance data is presented to prove that all the PMA is "completely converted to the inorganic form within days of dosing" and excreted from the body.

Since the literature clearly shows that PMA crosses the blood-brain and placental barriers and that the "*inorganic form*" of mercury that is present in the brain has a half-life of more than 20 years, petitioners find that all this letter has established here is that the level of "*inorganic mercury*" in the brain should be even higher than it is for the injection-dosed ethyl mercury compound Thimerosal, which recent (2004)

experiments in developing baby monkeys, reported in 2005, have shown is up to three (3) times higher than for the same level of orally dosed methylmercury hydroxide.<sup>288</sup>

Moreover, we find your “*Thus, the toxicity caused by PMA is similar to inorganic mercury, with the kidney as the target organ*” contradicts Clarkson,<sup>289</sup> who stated:

“The fact that much lower dietary doses of phenylmercury than of inorganic mercury can lead to the same degree of damage can be quantitatively accounted for by the difference in efficiency of gastrointestinal absorption of the two compounds” –

clearly indicating that the toxicity of PMA differs from that of “*inorganic mercury.*”

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

Furthermore, consulting the J.T. Baker’s year-2000 MSDS for PMA, petitioners find, under “**Emergency Overview,**” that this MSDS (see **Petitioners’ Table 3**) states, with underlining added for emphasis:

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

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

Based on the preceding, petitioners must conclude that: **a)** your letter’s characterization of PMA is, *at best, knowingly* misleading and **b)** PMA’s toxicity is “similar” to that of Thimerosal.

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<sup>288</sup> 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.

<sup>289</sup> Clarkson TW. The biological properties and distribution of mercury. *Biochem J.* 1972 Nov; 130(2): 61P-63P.

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

While petitioners see where the FDA obtained the value the letter states, we note that, since this NOEL value was derived from a rat study, in 1996, the EPA<sup>290</sup> reported that the ADI value that should be used in humans is “0.08  $\mu\text{g}/\text{kg}/\text{day}$ ” for PMA, a value “two” orders of magnitude lower than the one the FDA chose to use.

Deferring to the EPA’s understanding of the toxicity differences between rats and humans, petitioners find that this “0.08  $\mu\text{g}/\text{kg}/\text{day}$ ” is the value that should have used in any safety calculation for humans, and not the “8.4  $\mu\text{g}/\text{kg}/\text{day}$  PMA” for rats that the FDA elected to use.

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

Here, petitioners can only agree with the letter’s assessment that the most conservative value should be used for “risk estimation,” but again note that this value is the 1996 EPA ADI value of “0.08  $\mu\text{g}/\text{kg}/\text{day}$ ” for PMA for humans.

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

<sup>290</sup> <http://www.epa.gov/iriswebp/iris/subst/0089.htm>

*nostril every 4 hours for a total of 36 actuations per day, 0.07 ml/actuation, resulting in a total daily PMA exposure of 0.05 mg. Because mercury accounts for 86% of PMA by molecular weight, the daily exposure to mercury from this product approximates 43.34 µg/day or 0.87 µg/kg/day, assuming a 50-kg individual. Thus, the NOEL dose from the two year study in rats provides a 9.7-fold safety factor compared to the maximum human exposure if the maximum recommended dosage as labeled was used chronically, assuming that intranasal exposure in humans is comparable to dietary exposure in rats.”*

The petitioners have no problem with your calculated dose.

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

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

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

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

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

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

*“There are currently no pharmacokinetic data available to support this assumption; however, accumulation of mercury following chronic use is not expected due to the relatively quick clearance of inorganic mercury.”*

Again, all that has been demonstrated in the studies you cite is rapid clearance from the blood and urine and not rapid or, *more importantly*, complete clearance from the body.

**[Note:** As human studies have reported,<sup>291</sup> the “*inorganic mercury*” that is generated in the brain probably has a “20-plus-year” half-life – clearly indicating slow clearance of “tissue bound” inorganic mercury.]

We remind you that, *in spite of a “7-day” half-life in the blood*, Burbacher et al.<sup>292</sup> noted, *in a study on developing baby monkeys*, the half-life of the organic mercury in the brain was about a month, and there was a significant long-term accumulation (> 4 months) of “inorganic mercury” from the brain’s metabolizing that organic mercury into inorganic mercury.

*“There are currently no pharmacokinetic data available to support this assumption; however, accumulation of mercury following chronic use is not expected due to the relatively quick clearance of inorganic mercury.”*

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<sup>291</sup> Based on human autopsy studies on accident victims, the half-life (“half-time”) for “inorganic mercury” in the brain was found to be 22 years. [Sugita M. The biological half-time of heavy metals. The existence of a third “slowest” component. *Int Arch Occup Environ Health* 1978; 41(1): 25–40.]

<sup>292</sup> 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.

Again, all that has been demonstrated in the studies you cite is a rapid clearance of the mercury compound dosed from blood and urine, and not rapid or, *more importantly*, complete clearance from the body, including the brain.

Moreover, as *human studies have reported*,<sup>293</sup> the “*inorganic mercury*” that is generated in the brain probably has a “20-plus-year” half-life – clearly indicating slow clearance of “tissue bound” inorganic mercury.

We again remind you that, *in spite of a “7-day” half-life in the blood*, Burbacher et al.<sup>294</sup> noted, *in a study on developing baby monkeys*: **a)** the half-life of the organic mercury in the brain was about a month and **b)** there was a significant long-term accumulation (> 4 months) of “inorganic mercury” from the brain’s metabolizing that organic mercury into inorganic mercury.

*“In addition, these products are labeled for adults and children ages 6 years and older. For children under 6, the labeling states to ‘consult a doctor.’ Therefore, children under 6 are less likely to have any exposure to these products at all, or at least to be exposed with medical supervision to help ensure that the exposure is not excessive.”*

Given: **a)** the exposure level in 6-year olds can easily be > 25 times the EPA’s safe ADI and **b)** developing children have been shown to be more sensitive to being poisoned by mercury than adults, we find your reassuring remarks are unconvincing.

*“PMA is used in five prescription ophthalmic ointments. Based on the three ophthalmic ointments for which PMA concentration appears on drug product listing forms, the concentration is 0.0008% in these products. Because mercury is present in PMA at a level of 86%, based on molecular weight, the maximum mercury concentration in PMA-containing ophthalmic products is approximately 0.00069%. The recommended usage for these products is 1 cm ribbon in each eye four times a day. At a volume of 500 µl per application, the total daily exposure to mercury would be 27.5 µg/day or 0.55 µg/kg/day in a 50-kg person. Thus, the NOEL dose from the two year study in rats provides a 15-fold safety factor compared to the maximum human exposure.”*

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<sup>293</sup> Based on human autopsy studies on accident victims, the half-life (“half-time”) for “inorganic mercury” in the brain was found to be 22 years. [Sugita M. The biological half-time of heavy metals. The existence of a third “slowest” component. *Int Arch Occup Environ Health* 1978; 41(1): 25–40.]

<sup>294</sup> 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.

As was the case for the nasal sprays, petitioners agree with your dose calculations.

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

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

Therefore, you should have required/require the manufacturers of these products to have proven/prove safety in appropriate scientifically sound and appropriate toxicological tests, including reproductive toxicity tests of the formulation in, *minimally*, a mammalian animal model having comparable mercury-poisoning sensitivity as mercury-poisoning susceptible humans ("non-excretors") or, *better*, a susceptible primate species, with a dose 100 times the maximum dose allowed on the label so that the extrapolation to humans would be much more valid than extrapolating from the rat species commonly used for toxicity testing, which is known to be less than accurate in many cases or, *as is the case here*, requires a large multiplier (100 in this case) to convert from a "NOEL" in a short-term toxicity study on "rats" to a safe daily level ("ADI" in this case) for humans.

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

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

**[Note: Text continues on page P-302.]**

## Petitioners' Table 3 – Text from J.T. Baker MSDS

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

### PHENYLMERCURIC ACETATE

#### 1. Product Identification

**Synonyms:** (Acetato) phenyl mercury; acetoxypennymercury; PMA; PMAC; PMAS  
**CAS No.:** 62-38-4  
**Molecular Weight:** 336.74  
**Chemical Formula:** (CH<sub>3</sub>COO) HgC<sub>6</sub>H<sub>5</sub>  
**Product Codes:** T781

#### 2. Composition/Information on Ingredients

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

#### 3. Hazards Identification

##### Emergency Overview

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

##### Potential Health Effects

###### Inhalation:

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

###### Ingestion:

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

###### Skin Contact:

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

###### Eye Contact:

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

###### Chronic Exposure:

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

###### Aggravation of Pre-existing Conditions:

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

#### 4. First Aid Measures

**Inhalation:**

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

**Ingestion:**

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

**Skin Contact:**

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

**Eye Contact:**

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

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#### 5. Fire Fighting Measures

**Fire:**

Flash point: > 38C (> 100F)

Combustible solid.

**Explosion:**

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

**Fire Extinguishing Media:**

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

**Special Information:**

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

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#### 6. Accidental Release Measures

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

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#### 7. Handling and Storage

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

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#### 8. Exposure Controls/Personal Protection

**Airborne Exposure Limits:**

- OSHA Acceptable Ceiling Concentration:

mercury and mercury compounds: 0.1 mg/m<sup>3</sup> (TWA), skin

- ACGIH Threshold Limit Value (TLV):

inorganic and metallic mercury, as Hg: 0.025 mg/m<sup>3</sup> (TWA) skin, A4 Not classifiable as a human carcinogen.

- ACGIH Biological Exposure Indices:

total inorganic mercury in urine (pre-shift): 35 ug/g creatinine;

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

**Ventilation System:**

A system of local and/or general exhaust is recommended to keep employee exposures below the Airborne Exposure Limits. Local exhaust ventilation is generally preferred because it can control the emissions of the contaminant at its source, preventing dispersion of it into the general work area.

Please refer to the ACGIH document, *Industrial Ventilation, A Manual of Recommended Practices*, most recent edition, for details.

**Personal Respirators (NIOSH Approved):**

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

**Skin Protection:**

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

**Eye Protection:**

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

**Other Control Measures:**

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

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**9. Physical and Chemical Properties**

**Appearance:** Coarse yellow-white, hygroscopic powder.

**Odor:** Acetic acid odor.

**Solubility:** 0.16g in 100g of water.

**Density:** No information found.

**pH:** No information found.

**% Volatiles by volume @ 21C (70F):** 0

**Boiling Point:** Not applicable.

**Melting Point:** 149C (300F)

**Vapor Density (Air=1):** No information found.

**Vapor Pressure (mm Hg):** 0 @ 20C (68F)

**Evaporation Rate (BuAc=1):** 0

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**10. Stability and Reactivity**

**Stability:** Stable under ordinary conditions of use and storage.

**Hazardous Decomposition Products:** Carbon dioxide and carbon monoxide may form when heated to decomposition. Mercury compound may also be volatilized.

**Hazardous Polymerization:** Will not occur.

**Incompatibilities:** Strong oxidizing agents, sulfur, ammonia.

**Conditions to Avoid:** Heat, flames, ignition sources and incompatibles.

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**11. Toxicological Information**

**Toxicological Data:**

Oral rat LD50: 41 mg/kg. Irritation, standard Draize, rabbit, eye: 50 ug/24H, severe. Investigated as a tumorigen, mutagen, reproductive effector.

**Reproductive Toxicity:**

All forms of mercury can cross the placenta to the fetus, but most of what is known has been learned from experimental animals. See Chronic Health Hazards.

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

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

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## 12. Ecological Information

### Environmental Fate:

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

### Environmental Toxicity:

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

## 13. Disposal Considerations

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

## 14. Transport Information

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

Proper Shipping Name: PHENYLMERCURIC ACETATE

Hazard Class: 6.1

UN/NA: UN1674

Packing Group: II

Information reported for product/size: 25G

### International (Water, I.M.O.)

Proper Shipping Name: PHENYLMERCURIC ACETATE

Hazard Class: 6.1

UN/NA: UN1674

Packing Group: II

Information reported for product/size: 25G

## 15. Regulatory Information

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

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

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

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

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

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

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

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

Chemical Weapons Convention: No TSCA 12(b): No CDTA: No