DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Food and Drug Administration
Rockville MD 20852-1448

Paul G. King, Ph.D., and Other Representatives for CoMeD
Coalition for Mercury-free Drugs
33A Hoffman Avenue
Lake Hiawatha, NJ 07034-1922

Re: Docket Number 2007P-0331/CP1

Dear Dr. King and Others:

This letter is in response to your citizen petition dated August 10, 2007, in which you asked the Secretary of Health and Human Services or the Commissioner of the Food and Drug Administration (FDA) to take numerous actions pertaining to vaccines and other FDA-regulated products containing thimerosal or other mercury-based preservatives. We apologize for the delay in responding to the petition. After review and consideration, we deny the petition for the reasons stated below in this response.

As a preliminary matter, we note that your petition contains many of the very same arguments and studies presented in your July 30, 2004 citizen petition to which we responded on September 26, 2006 (FDA's 2006 response or our 2006 response). Because we have previously addressed these arguments and studies in our 2006 response, we have, where possible, limited our response to those arguments and/or studies that were not otherwise raised in your July 30, 2004 citizen petition.[1] We first address the underlying basis for all the actions you request: your contention that all licensed and approved products containing thimerosal have not been proven safe to the extent required by law. The first part of our discussion explains how FDA came to the conclusion that those licensed and approved products are safe. The second part explains why the studies on which you rely do not support your contention.

Here is an outline of our response:

I. LICENSED AND APPROVED PRODUCTS ARE SAFE
- A. The Products At Issue Were Shown To Be Safe Prior to Licensure or Approval
- B. Thimerosal is Safe for Use as a Preservative and Where There are Trace Amounts in the Final Product Resulting from the Manufacturing Process
  1. The effectiveness of thimerosal as a preservative was ascertained in prelicensure studies
  2. Thimerosal is effective as a preservative and does not function as an adjuvant
  3. The preclinical safety of thimerosal as a preservative and in trace amounts was ascertained in prelicensure studies
     - a. Preclinical toxicity studies
     - b. Animal models
     - c. Safety margin
  4. Clinical safety

[1] In other instances we considered it necessary to refer to the information contained in our 2006 response.

DISUSSION

I. LICENSED AND APPROVED PRODUCTS ARE SAFE

A. The Products At Issue Were Shown To Be Safe Prior to Licensure or Approval

The Public Health Service Act (PHSA), 42 U.S.C. §§ 201, et seq., authorizes FDA to license vaccines and other biological products if they have been demonstrated to be "safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i). In order to receive a license, an applicant must submit, safety, purity, and potency; a full description of manufacturing methods; data establishing the product's stability through the dating period; and a representative sample of the product (21 CFR 601.2(a)). Similarly, before approving a non-biologic drug, FDA must determine, based on its review of the clinical trial and other data submitted by the product's sponsor, that the drug is safe and effective for its intended uses. 21 U.S.C. § 355(b); 21 CFR Part 314.

FDA biologics regulations define safety as "the relative freedom from harmful effects 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). In applying this regulatory standard, FDA must weigh the risks of a vaccine – indeed, the risk of any drug – against its benefits when determining whether the product is safe. If the benefits of the vaccine or other pharmaceutical product outweigh the risks of its side effects, then FDA finds the product is safe. Applying the 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. Thus, the determination of a product's safety is a relative rather than an absolute measurement, and FDA's judgment as to what is required to ascertain the safety of a product is within the agency's discretion and expertise.

You content that FDA, in essence, has abused its discretion by licensing and/or approving thimerosal-preserved products that have not been proven safe to the extent required by 21 CFR 610.15(a) – one of the many general provisions that apply to all biological products (page P-215 of your petition).

Section 610.15(a) provides, in pertinent part:

> All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient…. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product.

21 CFR [§] 610.15(a).

Contrary to your claim, the regulations do not require specific kinds of "toxicological proof" or specific "studies" to demonstrate sufficient nontoxicity to "all intended direct and indirect recipients under the worst-case dosing regimen with some appropriate safety factor.")page P-218 of your petition). Rather, the regulations merely articulates the general safety standard by which all ingredients, preservatives, diluents, and adjuvants in biological products are to be scientifically evaluated by FDA, without specifying any method by which such safety must be shown. Furthermore, it does not require specific testing of individual ingredients and does not define "sufficiently nontoxic" or "will not be toxic to the recipient." Therefore, FDA is given deference in interpreting 21 CFR 610.15(a), and hence, has discretion in determining whether a manufacturer has demonstrated that a preservative is "sufficiently nontoxic" and that the biological product "will not be toxic to the recipient."

In making a determination about the safety of preservatives, the agency evaluates whether a preservative contained in a biological product is at such levels that the finished product itself, when used at the recommended dose, is not toxic to the recipient (see Section I.B.3.a. for further discussion). As detailed in FDA's 2006 response, and further explained below, FDA has applied sound scientific judgment in evaluating the products at issue and has repeatedly found that the vaccines and other products currently being marketed that contain thimerosal as a preservative are safe within the meaning of the PHSA, the Federal Food, Drug and Cosmetic Act (FDCA), and their implementing regulations.

B. Thimerosal is Safe for Use as a Preservative and Where There are Trace Amounts in the Final Product Resulting from the Manufacturing Process

1. The effectiveness of thimerosal as a preservative was ascertained in prelicensure studies

You state that thimerosal is less than effective as a preservative in drug products and you have cited a number of references in your argument. Preservatives are added to vaccine formulations to prevent the growth of bacteria or fungi that may be inadvertently introduced into the vaccine during use. In some cases, preservatives are used during the manufacturing process (e.g., in buffers and column washes) to prevent microbial growth and to control bioburden. The regulations require that, with certain limited exceptions, preservatives must be added to multidose vials of vaccines (21 CFR 610.15(a)). In fact, tragic consequences have followed from the use of multidose vials that did not contain a preservative and have served, in part, as the impetus for this requirement.[2]

The regulations do not, however, provide a definition of "preservative." A definition of a preservative (antimicrobial effectiveness) that has been used by FDA for vaccines and other biologicals is found in General Chapter <51> "Antimicrobial effectiveness testing" of the U.S. Pharmacopeia (USP).[3] This is a functional definition, wherein the final formulation of he vaccine, which includes the preservative, I challenged with specified quantities of the following organisms: *Candida albicans*, *Aspergillus niger*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The test sample, which is the preservative containing the vaccine plus

[2] Wilson GS., The Hazards of Immunization. New York, the Athlone Press, 1967, pp 75-84
[3] United States Pharmacopeia [26th ed.] Rockville, MD United States Pharmacopeia, 2007; USP 31/NF 26

the microorganism, is incubated at certain temperatures and the number of viable microorganisms is determined at days 7, 14, 21, and 28. The vaccine passes the antimicrobial effectiveness test when the acceptance criteria are met. It is important to note that the individual vaccine components and ingredients, by themselves, are not tested for antimicrobial effectiveness, it is only the final formulation that is tested.

This "Antimicrobial effectiveness test" is performed as part of the prelicensure assessment of every vaccine that contains thimerosal as a preservative. The test, as well as test results, are detailed in the Biologic License Application (BLA) for the particular product submitted by the vaccine manufacturer and evaluated by FDA scientists. In other words "proof of preservative effectiveness" supporting the use of thimerosal, or any preservative, as an effective multidose vial preservative is contained in the license application for the particular product.

However, preservatives cannot completely eliminate the risk of bacterial or fungal contamination of vaccines; moreover, preservatives do not address any potential viral contamination. As you have noted,[4] the scientific literature contains reports of bacterial contamination of vaccines despite the presence of a preservative, emphasizing the need for meticulous attention to the technique used in withdrawing vaccines from multidose vials as well as conditions of storage for the open vials. While no currently available preservative has been shown to be 100% effective, today's licensed vaccines containing thimerosal meet the requirements for a preservative as set forth in the United States Pharmacopeia.

2. Thimerosal is effective as a preservative and does not function as an adjuvant

You allege that FDA has cited no studies or other evidence to overcome the evidence, in your view, found in the paper by Setler, et al. (your footnotes 96, 269, 298 and 325) and that FDA has not responded to, nor considered, the evidence presented with regard to the "lack of effectiveness of 0.01% thimerosal as a preservative in vaccine." (page P-267 of your petition). On the contrary, FDA reviewed and responded to the findings by Setler, et al. (see page 17 of FDA's 2006 response). In particular, we noted the authors' overall conclusion that "no other preservatives that are currently available are **as safe and effective as thimerosal**." (emphasis added).

Furthermore, you claim that thimerosal appears to function as an immune system "adjuvant," despite not being labeled as such (page P-11 of your petition). Presumably, you are using the term "adjuvant" to describe an observed effect of thimerosal on induction of cytokine secretion in cell culture experiments and effects on serum antinuclear antibodies in genetically susceptible mouse strains (your footnotes 15(a) through (d), and 223(a) through (d)). However, in the context of immunology, the term "adjuvant" is used in the scientific community to describe a substance that in combination with a specific antigen produces more immunity that the antigen alone.[5] Thus, as we explained in our 2006 response, adjuvants are compounds added to a vaccine antigen to specifically enhance the immune response induced by the vaccine antigen. Thimerosal does not serve such a function, i.e., thimerosal does <u>not</u> enhance the vaccine antigen's immune-inducing response, and is <u>not</u> used as an adjuvant in any vaccines. The

[4] E.g., your footnotes 35, 40, 42, 94, 96, 106, 269, 270, 271, 272, 298, 325, 326, 327, 328, 329, 330.
[5] Ramon G., Procedures pour accroitre la production des antitoxins. Ann. Inst. Pasteur 40, 1926 pp 1-10.

labeling of U.S. licensed vaccines contains information about reduced or trace levels of thimerosal, presence of thimerosal as a preservative, or absence of thimerosal; the labeling does not refer to thimerosal as an adjuvant.[6]

3. The preclinical safety of thimerosal as a preservative and in trace amounts was ascertained in prelicensure studies

a. Preclinical toxicity studies

Your primary argument[7] is that FDA is violating its own regulations, 21 CFR 610.15(a), by not conducting or requiring specific toxicological testing of thimerosal. You state that FDA has "not addressed the fundamental petition issue of compliance with 21 CFR 610.15(a), much less proven that the biological drug product manufacturers are not somehow required to comply with this binding regulation" (page P-430 of your petition) (emphasis omitted). As described in section I.A. above, 21 CFR 620.15(a) only requires that any preservative contained in a biological product will be at such levels that the finished product itself, when used at the recommended dose, "will not be toxic to the recipient." Thus, 21 CFR 610.15(a) does not require specific testing of individual ingredients, does not specify a particular method by which safety must be shown, does not define "sufficiently nontoxic," and dose not define "will not be toxic to the recipient." Preservatives are not to be examined in isolation, as you argue, rather, 21 CFR 610.15(a) specifically directs that preservatives be examined in the context of the overall product and the recommended dose. Even when toxicology studies are mentioned in other contexts, such as in 21 CFR 312.23, pertaining to the content and format of an Investigational New Drug (IND) application, the regulation gives the sponsor discretion to use whichever approach or testing method is appropriate for a particular product. For example, 21 CFR 312.23(a)(8), states that the "kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations."

You have stated repeatedly that FDA has not provided "scientific proof" for the safety of thimerosal when used at doses and under the conditions of use regarding drug products, in particular, vaccines. As we explained in our 2006 response, all of the U.S. licensed vaccines on the market today went through the FDA's thorough approval process and were found to be safe and effective for their intended uses. The approval process requires the drug sponsor to establish, through carefully controlled nonclinical and clinical trials and other data, that the product is safe and effective for each of its intended uses. In other words, "scientific proof" of the safety is derived from the prelicensure studies, the results of which are described in the sponsor's new drug application (NDA) or BLA, and assessed by FDA in determining whether the application can be approved.

[6] For further information about labeling of US licensed vaccines see www.fda.gov/cber/vaccine/licvacc.htm.

[7] Pages P-10, P-13, P-101, P-104, P-106, P-107, P-127, P-129, P-130, P-131, P-157, P-172, P-173, P-175, P-176, P-182, P-183, P-184, P-215, P-218, P-222, P-223, P-226, P-227, P-236, P-253, P-255, P-262, P-264, P-282, P-283, P-311, P-312, P-321, P-322, P-332, P-337, P-339, P-343, P-359, P-371, P-380, P-381, P-385, P-389, P-392, P-393, P-394, P-396, P-397, P-398, P-405, P-411, P-413, P-418, P-426, P-428, P-429, P-430, P431, P432, P-433, P-434, and P-435 of your petition.

Specifically, with respect to toxicity, prior to proceeding to clinical trials, sponsors conduct carefully designed nonclinical toxicology studies in animal models using the proposed clinical product and formulation to evaluate the potential of the product to cause harm in the animal. Depending on the product under consideration, these nonclinical studies can range from acute, repeat dose chronic toxicity studies, and in certain cases, mutagenicity and carcinogenicity assessments. Only if FDA determines, based on these initial preclinical assessments, that it is safe to proceed to clinical trials, is the sponsor permitted to initiate them.

In addition, particularly if the product is to be administered to a population that includes females of childbearing age, sponsors conduct reproduction toxicity studies to evaluate the potential of the product to cause harm to the pregnant mother or the developing fetus.

b. Animal Models

As we stated in our 2006 response, "[p]rior 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." You argue that, with this statement FDA "explicitly proclaims that animal models are valid for evaluating the toxicity of thimerosal in vaccines" (pages P-332-P-333 of your petition). As stated in FDA's 2006 response, toxicology studies using currently available animal models are a very important and critical tool to assess the preclinical safety of the product. However, as we discussed, currently available animal models are limited in their ability to detect rare toxicities or specific toxicities that may occur in a particular human subpopulation. FDA supports the goal of developing predictive models for nonclinical assessments[8] and is working with manufacturers to develop better animal models and assays to measure activity and potential drug-induced toxicity at an early stage of product development. However, to date there are no relevant models that reliably predict that a vaccine, or an ingredient in a vaccine, may cause specific adverse events such as neurodevelopmental disorders.

You suggest use of "susceptible animals to establish that a mercury-based preservative or a mercury-containing component in the formulation is "sufficiently nontoxic." In particular you suggest SJL mice as a model, because, according to your statement, 0.01% thimerosal levels have been proven in this animal model to "elicit the same etiology as 'autism spectrum disorder' and 'alter the brain structures in the exposed mice" (pages P-5 and P-7 of your petition). You have cited a study by Hornig, et al. (2004) (your footnotes 7 and 202) in which the authors concluded that the SJL[/J] mouse provides a "model for investigating thimerosal-related neurotoxicity." Furthermore, you assert that the work of Hornig, et al. (2004) is important because these investigators were able to "duplicate[:] a) the symptoms and b) altered brain structures that have been found and reported when developing children are mercury poisoned." (page P-330 of your petition)

You state that the results presented by Hornig et al. (2004) "proved that using Thimerosal preserved vaccines does poison newborns who, for whatever reasons, are 'susceptible' to being mercury poisoned" (page P-331 of your petition) and that the Hornig, et al. findings provide "direct evidence (proof) that thimerosal preserved vaccines can cause brain damage

[8] See Critical Path Initiative, 69 Federal Register 21839, April 22, 2004.

mimicking many of the symptoms, behaviors, and/or brain-structure abnormalities seen in children diagnosed with severe neurodevelopmental disorders" (page P-331 of your petition). Finally, you contend that Hornig, et al (2004) "identified an animal model, SJL/mice, which can be used to study the toxicity of thimerosal at low levels in individuals that **are known to be susceptible to mercury poisoning**" (page P-331 of your petition) (emphasis added).

You urge FDA to use SJL/J mice as one of the animal models to demonstrate that a finished formulation is, as you state, "sufficiently nontoxic" because, according to you, "these animals have clearly proven their 'ability to detect rare toxicities, or specific toxicities that may occur in a human subpopulation' when it comes to mercury poisoning by Thimerosal or other mercury-based compounds" (pages P-337-P-338 of your petition) (emphasis omitted). You state that these mice "are or, seem to be, appropriately predictive of Thimerosal toxicity in susceptible humans" and you are rejecting, as you see it, "FDA's unsupported assertion here concerning the lack of a suitable model" (page P-338 of your petition) (emphasis omitted).

In addition, you state that these animals "have proven that there is a mercury-poisoning risk from Thimerosal-preserved vaccines dosed according to the 2001 US national childhood vaccination schedule." (page P-339 of your petition). You assert that the SJL/J mouse model has "been shown to be a potentially valid animal model for assessing the 'neurotoxic hazard posed by' Thimerosal … to the developing brain in susceptible individuals. …", (page P-340 of your petition). Finally you conclude that the SJL/J mice may (emphasis in the original) be used to "(e)establish a 'sufficiently nontoxic …'level of Thimerosal exposure to [sic; for] susceptible fetuses, neonates, babies, toddlers, preschoolers, children of school age, and adolescents. …", to "[e]stablish the 'no effect' level in susceptible individuals for Thimerosal or other mercury compounds. …" and to "[m]eet the government's statutory mandate to reduce the risk of adverse reactions in childhood vaccines set forth in 42 U.S.C. Sec. 300aa-27(a)(2)' (page P-341 of your petition).

Based on more recent studies, FDA concludes that SJL/J mice are not an appropriate animal model for thimerosal developmental neurotoxicity studies. We refer you to a study by Berman, et al. (2007), entitled "Low Level Neonatal Thimerosal Exposure: Further Evaluation of Altered Neurotoxic Potential SJL Mice."[9] Berman, et al. (2007) reexamined the findings by Hornig, et al. (2004), i.e., that low level thimerosal exposure to SJL/J mice produced altered brain development. Berman, et al (2007) conducted a follow-up study to evaluate whether altered immune system function may be a factor influencing vulnerability of the developing nervous system to thimerosal and to evaluate if the SJL/J mouse strain provides a sensitive model for thimerosal developmental neurotoxicity studies. The investigators used experimental procedures that closely followed those employed by Hornig, et al. (2004). However, in contrast to Hornig, et al. (2004), the study by Berman, et al. (2007) was more comprehensive because it added a dose-ranging component to the study design, used improved testing methodologies and expanded data collection by adding several measures, such as tests of social interaction, sensory gating and anxiety to assess behavioral domains considered relevant to core deficits in neurodevelopmental disorders.

[9] Berma, R., et al., Low Level Neonatal Thimerosal Exposure: Further Evaluation of Altered Neurotoxic Potential in SJL Mice. Toxicol. Sci. 2007;101(2),249-309.

Notably, the study by Berman, et al. (2007) did not reproduce the same results as those reported by Hornig, et al. (2004) and does not support the conclusions by Hornig, et al. (2004), namely that thimerosal exposure patterned after childhood vaccination schedules alters morphology of the hippocampus in autoimmune-susceptible SJL/J mice. To the contrary, Berman, et al. (2007) found no evidence that exposure to vaccine-associated levels of thimerosal, whether or not in combination with vaccine, resulted in abnormal somatic growth or altered the normal development or structure of the hippocampus. Berman, et al. (2007) reported that the overall pattern of results of their study does not indicate marked or pervasive neurotoxicological deficits in neonatal SJL/J mice following injections of vaccine-associated levels of thimerosal. In addition, and particularly relevant to human health concerns, Berman, et al. (2007) conclude that the current data do not provide support for the inference that neonatal thimerosal exposure is involved in the etiology of neurodevelopmental disorders that alter social behaviors such as autism. Additionally, the study finds that this mouse strain may not represent an unusually sensitive murine model of thimerosal neurotoxicity. However, the investigators point out that the hypothesis that genetic factors may predispose to higher risk from toxicant exposure, including various forms of mercury, is still important and needs further investigation.

In conclusion, the results of Berman, et al. (2007) do not demonstrate that SJL/J mice are a sensitive animal model for thimerosal developmental neurotoxicity studies. Furthermore, the results from this comprehensive study do not indicate pervasive neurodevelopmental toxicity following thimerosal injections in SJL/J mice at doses present in vaccines containing thimerosal as a preservative.

c. Safety margin

Next, we address your request that mercury-containing compounds be evaluated in toxicological studies using a "100X safety margin."[10] We assume that you are requesting the use of such safety factor because this value, 100X, is often described as being the product of one factor of 10 for interspecies (animal to human) variability in response to the toxicity, and another factor of 10 for intraspecies (human) variability in the same respect. However, the effect of a safety factor on the actual risk depends on the dose-response relationship and the exact of using a safety factor cannot be known with certainty. The selection of a safety factor in toxicological studies for drugs and biological products is based on the biological significance of the endpoint, uncertainties inherent in extrapolating information about adverse effects from toxicity studies in animals to human populations, and other judgmental factors. Hence, there is no a priori rule for using a 100X safety factor and exceptions to a safety factor of 100 are permitted in toxicology testing in accordance with the nature and extent of data available and the circumstances for use of the product. That said, in toxicology studies for vaccines, safety factors between 10X and 100X are usually used and may even exceed the 100X safety factor, e.g., in reproduction toxicity assessments.

[10] Pages P-6, P-7, P-8, P-9, P-11, P-13, and P-14 of your petition.

4. Clinical safety

a. Epidemiological studies

You have cited a number of studies that, in your view, establish a link between thimerosal exposure and adverse outcomes, including neurodevelopmental disorders in U.S. children.[11] First of all, we note that the studies by Counter, et al. (2002), Rury, (2006), Palmer, et al. (2006), and Windhman, et al.(2006) (your footnote 144, 145(a through c), 146) evaluated a potential association between environmental mercury exposure, and thus have little relevance to the issue of a potential association between the amount of thimerosal in vaccines administered to children and neurodevelopmental disorders, including autism. Of the remaining 13 references you cite in support of your contention of "established linkages between thimerosal exposure and adverse outcomes …," 11 were published by Dr. Mark Geier and his son, David Geier. As you are aware, the Institute of medicine (IOM) concluded that the studies published by Geier and Geier that were cited in the IOM 2004 report have "serious methodological flaws and their analytic methods [are] nontransparent, making their results uninterpretable, and therefore, non-contributory with respect to causality."[12] Other experts in the field confirmed this conclusion.[13]

We addressed the data published in Holmes, et al. (2003) (your footnotes 142, 148, 200, 303 and 339) in our 2006 response. As noted in that response, neither Holmes, et al. (2003), nor any other studies to our knowledge, have established that children who have relatively small amounts on mercury in their hair are unable to excrete mercury, and thus retain unsafe amounts of mercury in their bodies. Furthermore, we note that one of the principal shortcomings of that study was that the investigators only sampled hair and did not measure urinary or fecal excretion of mercury to support their hypothesis that autistic children do not metabolize and excrete mercury the way other children are able to.

To date, a number of epidemiological studies independently conducted by different investigators using various designs in different samples and countries, (e.g., Sweden, Denmark, United States, United Kingdom and Canada), all have consistently provided evidence of no association between thimerosal-containing vaccines and autism, despite the fact that different methods were used and different populations were examined.[14] With the exception of the study performed by

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[11] Your footnotes 141(a through k), 142, 143, 144, 145(a through c), 146.

[12] IOM (Institute of Medicine). Immunization Safety Review: Vaccines and Autism. Washington, D.C.: National Academy Press: 2004 (Executive Summary, at 7).

[13] Parker, et al., Thimerosal-containing vaccines and Autistic Spectrum Disorder: A Critical Review of Published Original Data. Pediatrics. 2004;114;793-804. Additionally, the Circuit Court for Baltimore City, in Blackwell, et al. v. Sigma Aldrich, et al., No. 24-C-04-004829, recently found that "Dr. Geier's epidemiological studies purporting to show an association between thimerosal-containing vaccines and autism were not conducted in accordance with generally accepted epidemiological methods" (Id. At 48) and "Dr. Geier's epidemiological studies are not generally accepted in the scientific community because they use methodology that is fundamentally flawed." (Id. At 30).

[14] Andrews, N et al., Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association. Pediatrics 2004;114;584-591; Stehr-Green, P., et al., Autism and Thimerosal-Containing Vaccines Lack of Consistent Evidence for an Association, Am. J. Prev. Med. 2003;25(2), 191-106; Madsen, et al., Thimerosal and the Occurrence of Autism: Negative ecological evidence from Danish population based data. Pediatrics 2003; 112; 604-606; Hivid, A., et al., Association Between Thimerosal-Containing Vaccine and Autism. JAMA 2003;290;13 1763-6; Fombonne, E., et al., Pervasive Developmental

Fombonne, et al., and reported in 2006, these [CDC-managed] studies were reviewed by the [CDC-contracted and directed] IOM, which concluded that they "**consistently provided evidence of no association between thimerosal-containing vaccine vaccines and autism**".[15] In addition, a recently published study by Schecter, et al., (2008), evaluated whether reduced exposure to thimerosal has been associated with a decrease in reported autism.[16] The researchers analyzed the California Department of Developmental Services (DDS) data to estimate time trends in children reported in California. The authors "found that the prevalence of autism for children reported to the DDS has continued to increase consistently for children born from 1989 through 2003, inclusive of the period when exposure to thimerosal containing vaccines declined. Moreover, since 2004, the absolute increase and the rate of increase in DDS clients 3-5 years with autism were higher than those in DDS clients of the same ages with any eligible condition, including autism." (Schechter, et al. 2008). In addition, the authors state that "[t]hese time trends are **inconsistent** with the hypothesis that thimerosal exposure is a primary cause of autism in California." Id. (emphasis added). These findings are consistent with other recent findings, e.g., Fombonne, et al. (2006).

Not only is there increasing and consistent compelling clinical evidence for a lack of association between thimerosal-containing vaccines and autism, in addition, a recent study published by Thompson, et al. (2007), does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and neuropsychological functioning in children aged 7 to 10 years old.[17] The study evaluated a total of 42 neuropsychological outcomes, including speech and language skills, executive function/attention, and ADHD (attention deficit hyperactivity disorder) symptomatology. The study was designed and interpreted with extensive input from independent outside consultants and the data set is publicly available. The study enrolled 1047 children between the age of 7 and 10 years (born 1993-1997) who had received thimerosal-containing vaccines and evaluated a possible association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period, and the first 7 months of life. The investigators concluded that their "study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the ages of 7 to 10 years." Thompson, et al., 2007). The few statistical significant associations that were detected were equally divided among better and poorer outcomes and may have been by chance findings due to the large number of statistical tests performed. According to the authors, one finding related to motor and phonic tics in boys may suggest that further study assessment is warranted.

Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations. Pediatrics 2006;118;e139-e150. Se also, your footnotes 137(e), 279, 284 and 315.

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

[16] Schechter, R., et al., Continuing Increases in Autism Reported to California's Developmental Services System. Arch Gen Psychiatry. 2008; 65(1):19-24.

[17] Thompson, WW., et al., Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years. N. Engl. J. Med 2007;367;1281-92.

In summary, the studies Fombonne, et al. (2006), Thompson, et al. (2007), and Schechter, et al. 208, all provide further support that thimerosal exposure of children from vaccines is not associated with neurodevelopmental disorders, including autism.

We note agreement " that, as written, the epidemiological studies cited here 'consistently provided evidence of no association between thimerosal-containing vaccines and autism.'" (page P-275 of your petition) (emphasis omitted). However, you discount these findings because, in your view, the studies "appear to have been designed not to find evidence of an association between the amount of thimerosal injected and the adverse outcomes observed" (page P-276 of your petition). Presumably in support of this statement, you reference a few articles that critique these epidemiological studies as being flawed (your footnotes 138, 139, 140, 280). We disagree with that assessment. The epidemiological studies cited by the FDA are accepted as valid by recognized scientific bodies and scientists and, despite some limitations, were generally well designed and appropriately analyzed (e.g., IOM report 2004 and Parker, et al. (2004)). In addition, the investigators of these studies have addressed methodological limitations in the discussion of their findings and considered any limitations in their overall interpretation of data. We maintain that the consistency of the findings observed from the epidemiological studies cited by us provide compelling evidence of no association between thimerosal-containing vaccines and autism, despite the fact that different methods were and different populations were examined.

b. Genetically susceptible individuals

You have cited a number of references[18] presumably to support your theory that some children, e.g., a genetically "mercury sensitive" subpopulation, may have a specific inability to metabolize mercury, and perhaps, these are the children at risk for developing autism spectrum disorders (ASD). You state "[g]rowing clinical evidence 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. [t]he mercury based preservatives in vaccines with which they have been immunized and/or b. [i]n utero, by the mercury-based preservatives in some of the drugs prescribed to and/or used by their mothers" (page P-82 of you petition) (emphasis omitted). In support of these claims you provided numerous references.[19] We provided a response to the studies conducted by Holmes, et al. (2003) and Bradstreet, et al. (2003) (your footnotes 147 and 148) in our 2006 response. Notably, exposure of children to thimerosal as a result of vaccination and/or preservative-containing drug(s) used by their mothers was not directly addressed or studied by these investigators. In addition, we have evaluated the additional articles you cite and find that none of them were designed to address your claim that "susceptible children" were damaged by "the mercury-based preservatives in vaccines with which they have been immunized" or suffered injury "in utero, by the mercury-based preservatives in some of the drugs prescribed to and/or used by their mothers." (page P-82 of your petition). In fact, most of the articles cited did not even mention the use of thimerosal preservative-containing vaccines and/or drugs containing preservative used by mothers of

[18] Section 15. Clinical evidence, pages P-82 through P-88 of your petition, your footnotes 147 through 159.
[19] Your footnotes 147, 148, 149, 150, 151(a) and (b), 152, 153, 154, 155, 156(a) and (b), 157, 158 (a through d), 159 (a through e), 160.

autistic subjects studied.[20] Thus, these studies present no direct evidence that thimerosal preservative or other components in a vaccine or drug product contribute to the development of ASD in genetically susceptible subpopulations.

There is, however, growing evidence that autism is largely a genetic disorder.[21] It is acknowledged that this does not rule out contributing environmental factors; however, based on the evidence presented to date, thimerosal preservative in vaccines or other drugs has not been shown to be a risk factor in the development of neurodevelopmental disorders, including ASD.

5. The government's use of methylmercury guidelines to estimate exposure levels for ethylmercury and evidence that ethylmercury is less toxic than methylmercury

You state that FDA inappropriately used the EPA's reference dose for methylmercury as a guideline for setting a level of exposure for ethyl mercury. At the time of the initial risk assessment in 1999, the use of a safety assessment for a related alkylmercurial was justified because guidelines for ethylmercury were not available. FDA stated there was uncertainty in applying guidelines for methylmercury to thimerosal (your footnote 235, www.fda.gov/cber/vaccine/thimerosal.htm#guid) At that time, lacking definitive data on the comparative toxicology of ethylmercury versus methylmercury, FDA considered ethylmercury and methylmercury equivalent in its evaluations. Since then, newer information indicates that the EPA reference dose may be an overly restrictive limit for ethylmercury[22] and suggests that the risk that occurs from transient ethylmercury exposure from vaccinations. The reasons for a lack of comparability are: 1) chronic uncontrolled exposures at low levels compared to small defined exposures; and 2) there is evidence that ethylmercury is less toxic in acute exposures than methylmercury.

Nearly all of the references cited in your petition for the toxicity of organic mercury are risk assessments of long-term uncontrolled dietary exposures to methylmercury as opposed to single or repeated, controlled, low-level intramuscular exposure, as would be the case for a subject receiving a thimerosal-containing vaccine. For example, MacMillan (1987) (your footnote 1) discusses the safety framework for neurobehavioral toxicity. The structure of this framework is based on long-term exposures of test animals to neurotoxic substances with the intent of determining no-observed-effect levels (NOEL), no-observed-adverse-effect (NOAEL) and lowest-observed-adverse-effect levels (LOAEL). The adverse effects measured are changes compared to control animals in a range of sensory, motor and behavioral test. This analysis leads to an acceptable daily intake (ADI) determination of the compound in question. The determination of an ADI is an amount of the neurotoxin that would be acceptable if the amount were received every day. Daily exposure to ethylmercury is not the

[20] E.g., your footnotes: 147, 150, 151(a), 151(b), 152, 153, 154, 155, 156 (b), 158 (a through d), 159 (a), 159(b through e), 160.

[21] Szatmari, P., et al., Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nature Genetics 2007; 39;3 319-328; Weiss, L. et al., Association between Microdeletion and Microduplication at 16p11.2 and Autism. N. Engl. J. Med. 2008;358;7 667-675

[22] Pichichero, M., et al., Mercury levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. Pediatrics, 2008;121;e208-e214; and Berman, et al., see our footnote 9 above.

pattern of human exposure from vaccinations, which normally occurs only intermittently, often only on an annual basis. You cite papers that discuss the problem of using biomarkers to estimate methylmercury exposures[23] and argue that the methylmercury reference dose may have been set too high. Recent studies have concluded that the benefits of eating fish may outweigh the risk associated with increased methylmercury exposure which implies that the reference dose for exposures that occur through fish may be too low.[24] The study by Rice, et al. (1996) (your footnote 4(d)) discusses the lessons for neurotoxicity from model compounds. This study is not applicable to the question of the safety of thimerosal, as ethylmercury was not one of the compounds discussed and methylmercury may not be a good model for ethylmercury based on the differences in pharmacokinetics and toxicity. The only reference citied in your petition that specifically deals with ethylmercury from a safety assessment perspective is the Assessment of Mercury Releases from the Russian Federation (2005). The standard for ethylmercury given in this document actually comes from a different document, the Hygienic Norm 2.1.5.689-98 (1995) issued by the Russian Ministry of Health. This Norm does not provide a safety assessment for ethylmercury, but rather merely lists a standard without a rationale for the level chosen. Even so, with respect to uncontrolled daily exposures to ethylmercury, this standard may be reasonable, but in the context of intermittent exposure to ethylmercury, it is not appropriate because exposures to ethylmercury from vaccination is neither uncontrolled, nor does it occur on a daily basis.

Toxicological risks from chemical substances are different when exposures are short-term compared to long-term. Exposure to methylmercury is long-term because of he continual exposure that humans receive in their diet and because of the relatively long half-life of methylmercury in the body compared to ethylmercury. Burbacher, et al. (2005) (your footnote 288) estimated the half-life of methylmercury in the blood of juvenile in the blood of juvenile non-human primates to be on the order of 21.5 days. The consequence of long-term, low-level exposures to methylmercury in humans is that the levels of methylmercury tend to reach a low, steady-state concentration in tissues. This long-term, low steady-state exposure to methylmercury contrasts with the short-term intermittent exposure to ethylmercury that individuals receive through vaccinations. The biological half-life of ethylmercury in blood in humans has been estimated to be between 7 days (Burbacher, et al., 2005, your footnote 288) and 3.7 days (Pichichero, 2008, our footnote 22). This relatively short half-life implies that ethylmercury is essentially cleared from the body after vaccination in as little as one month (Pichichero, 2008, our footnote 22).

There is evidence that ethylmercury is less toxic compared to methylmercury.[25] One reason for lesser toxicity of ethylmercury compared to methylmercury may be ethylmercury's shorter half-life, as discussed above. Animal toxicological studies of Magos, et al. (1985)[26] have shown that at comparable doses, ethylmercury is less toxic than methylmercury in rats. A plausible explanation for this observation could be the differential metabolism of ethylmercury compared to methylmercury in different tissues. Ethylmercury was [qualitatively] shown to be

[23] Your footnotes 4(a),(b), and (e), 260(a through c), 299(a), (b) and (e), 302, 336, 337, and 338.
[24] Mozzaffarian, D. and Rimm, E., Fish Intake, Contaminants, and Human Health, Evaluating the Risks and Benefits. JAMA 2006;296:15
[25] Clarkson, TW. And Magos, L., 2006, reference 112 on P-61 of your petition.
[26] Reference 61 on page P-57 of your petition.

more toxic to the kidney than to the brain (Magos, et al., 1985). These observations appear to rum counter to the observations of Tryphonas and Nielsen, (1973),[27] who compared intoxication of [young developing] pigs with methylmercury and ethylmercury. Intoxications at daily doses of 0.19 mg mercury (Hg) per kilogram [0.19 ppm] were apparently comparable for the two compounds, but dosages at 0.38 mg Hg per kilogram showed more lesions and neurological signs for ethylmercury [including death] compared to methylmercury [no signs, no deaths]. At still higher levels of exposure, 0.76 mg Hg per kilogram, both compounds caused lesions and neurological signs, but ethylmercury was reported to show them sooner than methylmercury. The results of Magos, et al. (1985) and Tryphonas and Nielsen (1973) appear to be at variance with one another, but their experiments differ. The first difference is the animal model (rat versus pig); the second difference is that Magos, et al. (1985) used a higher dose of the two alkylmercurials (8 mg Hg per kilogram); and the third difference is the duration of the experiments (5 versus 60 and 90 days).

Tryphonas and Nielsen (1973) conducted their experiments for [up to] 60 days with methylmercury and for [up to] 90 days with ethylmercury. Tryphonas and Nielsen (1973) report that the pigs receiving ethylmercury experienced significantly higher accumulations of mercury in the kidney compared to pigs receiving methylmercury, which is an observation that agrees with Magos, et al. (1985). The apparent neurotoxicological difference between the two alkylmercurials may be secondary to the long-term effects of compromised kidneys and liver damage in the ethylmercury-treated pigs. Both sets of experiments used multiple ethylmercury doses far in excess of that received in a vaccination on a daily basis, and the animals showed systemic symptoms of intoxication rather than neurotoxic symptoms. Other recent experiments that have exposed animals to doses of ethylmercury include those reported by Berman, et al. (2007)[28] with SJL mice. As discussed above, Berman, et al. (2007) failed to replicate the findings of Hornig, et al. (2004) that SJL mice are especially susceptible to ethylmercury exposures. The experiments reported by Berman, et al. (2007) show that for a vaccination schedule that mimics the doses of thimerosal received from childhood vaccines before thimerosal was removed, SJL mice had very little mercury in their system 24 hours after the last dose of thimerosal. This low level of mercury was observed even when some SJL mice received thimerosal doses that were 10 times the normal dose. These experiments are significant because they compare the performance of exposed mice in behavioral tests relevant to core deficits in neurodevelopmental disorders and do not find significant differences from controls.

Further evidence of lesser toxicity of ethylmercury compared to methylmercury in humans comes from two intoxications cited in Clarkson and Magos, (2006). An ethylmercury intoxication of an individual was reported by Pfab, et al. (1996)[29] where the victim ingested 83 mg/kg thimerosal. The victim had a reported blood mercury level of 14,000 µg Hg/L and experienced anuria, coma, polyneuropathy, and respiratory failure. The victim recovered with no permanent brain damage. This intoxication contrasts with a victim of methylmercury intoxication who was found to have a blood mercury level of 1840 µg Hg/ L and experienced

[27] Your footnote 5.
[28] Our footnote 9.
[29] Pfab, R., et al., Clinical Course, of Severe Poisoning with Thiomersal. Clinical Toxicology. 1996;34;4: 453-60.

similar symptoms to the ethylmercury intoxication victim. Unfortunately for the methylmercury victim, his symptoms did not resolve and the patient remained ataxic and dysarthric.[30]

Another factor related to the apparent lesser neurotoxicity of ethylmercury is the timing pf ethylmercury exposure. The earliest exposure to ethylmercury for a child occurs during an influenza vaccination from a multidose vial (if thimerosal-free influenza vaccines are not used) at six months of age; however, children are exposed to methylmercury from conception throughout their lives. A reference in your petition[31] discusses the neurobehavioral effects of developmental exposure to methylmercury. The analysis examines the effects of prenatal exposure of the fetus to methylmercury and argues for a reduction in the accepted reference dose. Gestation is a critical period of development of a child's brain, but exposure to ethylmercury during that period usually would occur only if the mother receives a thimerosal-containing influenza vaccine during pregnancy. In that event, the rapid elimination of ethylmercury by the mother provides a measure of protection for the fetus.

The nature of exposure to ethylmercury is different compared to the nature of the exposure to methylmercury. All the evidence of measurable harm to children from dietary methylmercury exposure comes from long-term exposures at levels far higher than those seen in the U.S. population. The intermittent low-level ethylmercury exposures that occur with vaccinations are not comparable to the long-term methylmercury exposures because ethylmercury is quickly cleared from the blood and never reaches a steady-state level. Furthermore, the neurotoxicity of ethylmercury appears to be less than that for methylmercury based on its shorter half-life in the body and differential metabolism in tissue.

You cite Sugita (1978)[32] in the context of risk of exposure to mercury in terms of the apparent long half-life of mercury in the human body. This reference does not appear to be relevant to the question of safety of ethylmercury as the results of the analysis do not distinguish ethylmercury from total mercury. The paper by Sugita (1978) estimates the half-lives of heavy metals based on differential equations of intake and excretion, and organ and tissue levels of total mercury from a sample of cadavers in Tokyo. The difficulty in interpreting Sugita's results for a half-life is that he bases his estimate on the tissue concentration of total mercury rather than distinguishing between organic and inorganic forms of mercury. It is known that different forms of mercury in the body have different half-lives and that without incorporating the different forms of mercury into the model and starting with data on the amounts of each form of mercury in the tissues and organs, it is difficult to interpret the results of this analysis in the context of a safety assessment for ethylmercury.

[30] Magos, L., Three Cases of Methylmercury Intoxication Which Eluded Correct Diagnosis. Arch. Toxicol. 1998;72: 701-705.
[31] Your footnotes 4(c), 261(a), 299(c).
[32] Your footnotes 11(b), 118(a), 192, 198, 263, 291, 293, and 341(a).

C. FDA has Taken Steps to Reduce Exposure to Thimerosal Despite Lack of Evidence of a Safety Concern

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

You have acknowledged that thimerosal either has been removed or the level has been reduced from [some] pediatric vaccine formulations (page P-15 of your petition). All vaccines manufactured since 2001 [that are] 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, rotavirus and varicella) have contained no thimerosal or only trace amounts with the exception of inactivated influenza vaccine. Prior to the government's initiative to reduce or eliminate thimerosal form childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first 6 months of life was 187.5 ug [sic; µg]. With the introduction of thimerosal preservative-free formulations of DTaP, hepatitis B, and Hib, the maximum cumulative exposure from routinely recommended childhood vaccines decreased to less than 3 ug [sic; µg] of mercury in the first 6 months of life. With the addition in 2004 [factually, 2002 and not 2004] of influenza vaccine to the recommended childhood vaccines, an infant could receive a thimerosal-containing influenza vaccine at 6 and 7 months of age. This potentially could result in a maximum exposure of 28 ug [sic; µg] of mercury during the first 7 months of life from thimerosal preservative-containing influenza vaccine. However, studies referenced in Section I.B.4.a. have not shown adverse outcomes in children that received thimerosal-containing childhood vaccines. Thus, it is unlikely that a child would suffer harm from the amounts of thimerosal preservative present in currently distributed vaccine products.

2. Adult exposure to thimerosal through vaccines has been reduced

As with pediatric vaccines, vaccine manufacturers have succeeded in reducing mercury exposure from thimerosal in vaccines for adolescents and adults. For example, all hepatitis B vaccines for adolescents and adults [in the USA] are [currently] free of thimerosal. Tetanus and Diphtheria toxoids (Td) vaccine, indicated for children 7 years of age and older and adults, is now available only as a thimerosal preservative-free formulation. These changes have been accomplished by reformulating products in single-dose vials that do not contain preservative. In addition, FDA has recently licensed two combination vaccines, composed of tetanus, diphtheria, and pertussis antigens (Tdap), a meningococcal conjugate vaccine, a zoster vaccine, and a human papillomovirus vaccine, none of which contain thimerosal. The thimerosal content of [most of the currently distributed] U.S. licensed vaccines, including those indicted for adolescents and adults, is available at http://www.fda.gov/cber/vaccine/thimerosal.htm

3. The Federal government has not increased the "mercury poisoning" of fetuses, infants, children, adolescents, and adults including pregnant women

You argue that "the FDA's rhetoric is a blatant attempt o 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" (page P-235 of your petition, emphasis omitted).

You state that the government's recommended vaccination policies have been designed to continue the unnecessary mercury poisoning of children by thimerosal by increasing the level of thimerosal derived to which some fetuses are exposed, by adding influenza vaccines to the recommended schedule in children 6-59 months of age, by failing to mandate that no vaccines contain thimerosal, and by thwarting the efforts of parent groups in various State and federal legislatures to implement legislation to restrict or ban thimerosal (pages P-239-P-240 of your petition).

You argue that rather than removing thimerosal from all childhood vaccines, the Federal government has raised the maximum level of thimerosal that infants may be exposed to because the CDC a) recommended immunization of children 6-23 months of age in 2002; b) extended these recommendations in 2006 to children 6-59 months of age; c) recommended in 2007, that children 6 months – 8 years who received only 1 dose in their first year receive 2 doses the following year; and d) recommended immunization of pregnant women with vaccine during all stages of pregnancy (page P-231-P-232 of your petition). You have provided your calculations on presumed exposure to mercury of children less than 60 months of age (i.e., up to 150 ug [sic; µg] mercury according to your calculations) from pre- and postnatal exposure to thimerosal-containing influenza vaccines (page P-237 of your petition). You further allege that "the government has knowingly failed to honor the 'eliminate from, or reduce thimerosal in all vaccines' goal" and has "ignored its original 1999 commitment to remove all thimerosal-containing childhood vaccines from the market" (page P-233 of your petition, emphasis omitted).[33]

Contrary to your assertion, the Centers for Disease Control and Prevention (CDC) issued an official recommendation for immunization of 6-23 month old children with inactivated influenza vaccine in 2004 and, not, as you state in 2002. In addition, your statement that the government failed to honor the goal to "eliminate or reduce thimerosal in all vaccines" is without merit. The joint statement issued by the American Academy of Pediatrics (AAP) and the Public Health Service (PHS) in July 1999, and agreed to by the American Association of Family Physicians (AAFP) later in 1999, established the goal of removing thimerosal as **soon as possible** from vaccines **routinely** recommended for infants. This goal was established as a precautionary measure. No evidence exists of any harm caused by low levels of thimerosal in vaccines (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4927a5.htm). The government has been very efficient in meeting this goal. In fact, within 2 years of issuance of this statement, thimerosal-free or thimerosal-reduced childhood vaccines were available. In addition, all thimerosal preservative-containing childhood vaccines that were still on the market reached the end of their shelf life by January 2003, and hence are no longer available on the market. Moreover, most vaccines recommended for adolescents and adults are available as thimerosal preservative-free formulations and, as discussed in Section I.D.3.g., thimerosal-free formulations of influenza vaccines are also available.

[33] Your footnotes 240,241, 242, 243, 244 and 245.

You argue that the Federal government, since 2002, has "[i]ncreased 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," "[a]llowed other 'Thimerosal preserved,' 'reduced Thimerosal' and 'trace Thimerosal' vaccines to also be administered to children, pregnant women, and nursing mothers," and "[l]icensed a new Thimerosal-preserved inactivated-influenza vaccine"[34] (page P-233 of your petition). Moreover, you state that the Secretary and FDA are knowingly "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" (page P-234 of your petition). You state further that the Federal government has added 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 (pages P-234 and P-235 of your petition).

Throughout your petition, you have cited numerous studies that evaluated outcomes in infants during epidemics of mercury poisoning, for example, those occurring in Iraq during the 1970s when seed grain treated with mercury fungicide was accidentally used to make bread. However, these references are mostly concerned with uncontrolled long-term dietary exposure as opposed to single or intermittent, controlled low levels of intramuscular exposure, as would be the case for a subject receiving a thimerosal preservative-containing vaccine. Thus, the data cited do not provide evidence that ethyl mercury at doses present in thimerosal preservative-containing vaccines causes the same or similar effects in fetuses or infants as was observed when humans ingested mercury-contaminated food daily over prolonged periods of time. You cite no data or other evidence demonstrating that an infant is "at risk" from "mercury poisoning" in utero **as a result of the mother's immunization with thimerosal preservative-containing vaccine**, or receiving any other thimerosal-containing drug. Also, and contrary to your assumption, all recently licensed influenza vaccines have been or are being evaluated in reproduction toxicity studies. Results available from these animal studies have not shown an adverse effect of the thimerosal preservative-containing influenza vaccine on the developing fetuses. In addition, recently published data by Thompson, et al. (2007), who evaluated prenatal exposure to thimerosal-containing vaccines in a clinical study, did not demonstrate any adverse outcomes in prenatally exposed children.[35]

You argue that FDA has failed to address, and has knowingly decided to ignore, the potential indirect infant mercury exposure from breast milk when nursing mothers are given thimerosal preservative-containing vaccine or other drug product while they are breast-feeding their infant children (pages P-228-P-230 of your petition). To the best of our knowledge, there are no data to suggest that a nursing infant may suffer "damage" from thimerosal-containing vaccine or other drug product administered to the mother. You have cited a study by Amin Zaki

[34] Your footnotes 241, 242, 243, 244, 245.

[35] Thompson W[W], et al., [Price C, Goodson B, Shay DK, Benson P, Hinrichsen VL, Lewis E, Eriksen E, Ray P, Marcy SM, Dunn J, Jackson LA, Lieu TA, Black S, Stewart G, Weintraub ES, Davis RL, DeStefano F; Vaccine Safety Datalink Team.] Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med. 2007 Sep 27; 357(13): 1281-1292.

showing that mercury may result in neurodevelopmental disorders in children (your footnote 238). Of note, these investigators evaluated mother and infant exposure to methylmercury during the Iraq epidemic of 1972, an outbreak of methylmercury poisoning as a result of consumption of contaminated homemade bread. Data derived from this study do not support a finding of "risk" to a breast-feeding infant from potential exposure to small amounts of ethylmercury contained in vaccines, representing a different form of mercury and administered to the mother by a different route and schedule.

Given current limited availability of thimerosal preservative-free influenza vaccine, children under 60 months of age, and for that matter, adults, may receive thimerosal preservative-containing influenza vaccine. However, data has shown that there is no known harm from thimerosal preservative-containing vaccines in children (see I.B.4.a.). In addition, your calculation regarding presumed exposure of children less than 60 months of age to 150 ug [sic; µg] mercury from thimerosal-containing influenza vaccines is unsubstantiated for several reasons. First, you have provided no data that showed that the in utero exposure levels of mercury in fetuses whose mothers may have received thimerosal-containing influenza vaccine during pregnancy corresponds to the actual amount of mercury in the vaccine formulation. Second your "specific dose calculations" appear not to take into consideration uptake, metabolism, and excretion of mercury in the mother who may have received a thimerosal preservative-containing influenza vaccine. Third, you have not taken into account uptake, metabolism, and excretion of thimerosal in infants who may have received a thimerosal preservative-containing influenza vaccine.

Recently published data demonstrate that the blood half-life of ethyl mercury in infants from thimerosal preservative-containing vaccines administered intramuscularly is short, i.e., the blood mercury half-life was calculated to be 3.7 days in young infants and returned to prevaccination levels by day 30. This short half-life of ethylmercury in blood of infants likely prevents build-up of mercury from occurring. Increased mercury levels were detected in stools after vaccination, suggesting that the gastrointestinal tract is involved in ethylmercury elimination.[36] In addition, little is known about tissue disposition of mercury in human infants and thus it is not at all established that inorganic mercury accumulates in the brain of these infants as you assert (page P-236 of your petition). As discussed in Section I.D.3.g., thimerosal preservative-free influenza vaccine formulations are available. Additionally, we note that influenza vaccination coverage in pregnant women and infants 6-23 months is low (approximately 15% and 33%, respectively).[37] Finally, there is no evidence that mercury exposure of children from thimerosal-containing vaccines at levels of 187.5 ug [sic; µg], when children received all vaccines according to the late 1990s' recommended childhood immunizations, were [sic; was] harmful; thus, it is highly unlikely that lower levels would cause harm (see Section I.B.4.a.).

You describe a "hypothetical mercury-retaining adult person" (page P-251 of your petition) by assuming that inorganic mercury from thimerosal preservative has a two-plus decades long half-life in a human. In support of this, you cite Sugita (1978) (your footnote 263) for the proposition that mercury has a long half-life in the human body. This reference does not appear to be relevant to the question of the safety of ethyl mercury because the results of the analysis do not

[36] Pichichero M, et al, Mercury levels in newborns and infants after receipt of thimerosal-containing vaccines. Pediatrics, 2008;121(2):e208-e214 (our footnote 22).

[37] See http://www.cdc.gov/flu/professionals/acip/coveragelevels.htm

distinguish ethylmercury from total mercury (see Section I.B.5.) nor is there documentation of adverse effects associated with exposures at these levels. Furthermore, you are assuming that this "hypothetical mercury-retaining adult person" may receive Menomune, even though this vaccine is not routinely recommended. In fact, a thimerosal preservative-free meningococcal conjugate vaccine is available and routinely recommended for immunization against meningococcal disease. Also, you include tetanus toxoid vaccine in these calculations. We note that the only thimerosal preservative-containing tetanus toxoid vaccine available in the U.S. is a product for booster use only. Moreover, this vaccine would be administered only in those rare instances where a person cannot receive aluminum. In all other situations, tetanus toxoids adsorbed vaccine or diphtheria and tetanus toxoid adsorbed vaccines are recommended, none of which contain thimerosal as a preservative. Finally, efforts are underway by the manufacturers and the government to increase the supply of thimerosal-free influenza vaccines. Thus, your assertions with regard to the exposure to mercury of adults from thimerosal in vaccines are speculative.

D. The Few Products That Still Contain Thimerosal are Safe

1. Plasma Derivatives

Multidose presentations containing thimerosal preservative have been discontinued for all licensed plasma derivative products, with the exception of the antivenoms [sic; antivenins] described below. All immune globulin preparations, including hepatitis B immune globulin and Rho(D) immune globulin preparations, are manufactured without thimerosal, and thimerosal-containing formulations are no longer available.

Four antivenoms [sic; antivenins] that contain thimerosal as a preservative remain on the market. They are pit viper (2), coral snake (1) and black widow spider (1) antivenoms [sic; antivenins]. Although FDA encourages manufacturers of licensed products to decrease the amount of thimerosal in those products, to develop manufacturing methods that do not use thimerosal, snake and black widow bites are dangerous and can cause serious morbidity and mortality. Removal of the product from the market by FDA would not be in the best interest of public health when no substitute products are available and when exposure to thimerosal at these levels has not been shown unsafe, especially since such action would be likely to result in severe illness and death. In fact, Wyeth Pharmaceuticals, Inc. has stopped manufacturing its pit viper and coral snake antivenoms [sic; antivenins], but the in-date product must remain available on the market because Wyeth's is the only licensed coral snake antivenom [sic; antivenin], and supplies of the other licensed pit viper antivenom [sic; antivenin] are not sufficient at this time. A list of mercury-free and mercury-containing plasma-derived products is posted at www.fda.gov/cber/blood/mercplasma.htm.

2. Thimerosal and phenylmercuric acetate (PMA) in nasal, ophthalmic, and otic drug products

FDA's position that mercury exposure from nasal, ophthalmic, and otic products is minimal and the products are safe as described in section 1.C.3 of FDA's 2006 response to petitioner's [s'] citizen petition of August 2004. FDA recognizes that these products are prescribed for repeated use over time. Thus, the FDA considered conservative use estimates in evaluating the safety of

these products and in determining what the mercury exposure from such products likely would be.

In our 2006 response, FDA stated that "PMA is an organic (aryl(form of mercury that is rapidly metabolized to an inorganic form of mercury…. The rapid conversion of PMA from the organic form to the inorganic form is an important factor in PMA's toxicity profile. Although organic methylmercury is detectable in experimental animals for weeks after a single injection, phenylmercuric salts are completely converted to an inorganic from within days of dosing (Clarkson 1972). The rapid clearance of inorganic mercury compared to organic methymercury helps to render the inorganic forms generally less toxic. Thus the toxicity caused by PMA is similar to inorganic mercury, with the kidney as the target organ."

In response to this, you state that after reviewing the limited literature on PMA, FDA failed to provide an accurate picture of PMA's toxicity (page p-290 of your petition). You further state that no clearance data was provided to prove that all PMA is completely converted to inorganic forms within days of dosing and excreted from the body (page P-290 of your petition). You counter that a different [Clarkson] paper (your footnote 289) contradicts FDA's statement that the toxicity caused by PMA is similar to inorganic mercury by citing Clarkson (1972) " '[t]he 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'" (page P-291 of your petition). You refer to unspecified literature, arguing that it shows PMA crosses the blood-brain and placental barriers, and that the inorganic form of mercury present in the brain has a half-life of more than 20 years. You argue that PMA, like thimerosal and other ethylmercury and methylmercury compounds, has the potential to damage the central nervous system in the fetus, child and adult. You conclude that FDA's 2006 response establishes that the level of inorganic mercury in the brain after exposure to PMA "should be even higher than it is for the injection-dosed ethylmercury compound Thimerosal" (page P-290 of your petition), and that experiments on developing monkeys have shown that inorganic mercury derive from thimerosal is up to three times higher than the same levels derived from orally dosed methylmercury hydroxide (Burbacher, et al., 2005, your footnote 288). You state that JT Baker's year 2000 material safety data sheet (MSDS) for PMA states that mercury compounds affect the kidney and the CNS, and can cause birth defects. You conclude that PMA's toxicity is "similar" to that of thimerosal and FDA's characterization of PMA is knowingly misleading.

We reject your assertions. The 1972 Clarkson paper cited by FDA,[38] as well as other papers,[39]indicates that phenyl mercury salts undergo complete breakdown to inorganic mercury within days. Your citation of another Clarkson paper[40] indicating that lower dietary doses of phenylmercury compared to inorganic mercury can lead to the same degree of damage does not change the conclusion that PMA is converted to inorganic mercury or that the toxicity profile differs. Rather this paper only indicates that the absorption efficiency of the two mercury forms

[38] Clarkson, T.W., The Pharmacology of Mercury Compounds. Annual Review of Pharmacology. 1972;12 375-406.
[39] Daniel, J.W., et al., The Metabolism of Phenylmercury by the Rat. Biochem J. 1972;129, 961-967; Miller, V.L. et al., Absorption, Distribution and Excretion of Phenylmercuric Acetate. Toxicol. Appl. Pharmacol. 1960;2 344-352; Gage, J.C., Distribution and Excretion of Methyl and Phenyl Mercury Salts. Brit. J. Ind. Med. 1964;21 197-202.
[40] Your footnote 289.

differs. This difference does not alter the overall safety evaluation of PMA, which was based on chronic toxicity studies in rats described in our 2006 response and referenced below.

Your statement that FDA's 2006 response establishes that the level of inorganic mercury in the brain after exposure to PMA should be even higher than it is for thimerosal is not supported by data. Nonetheless even with the distribution to the brain and rapid conversion to inorganic mercury, there is no consensus that inorganic mercury in the brain causes damage, in contrast to the known effects of methyl mercury. The cited study by Burbacher, et al. (your footnote 288) does show that levels in the brain are approximately two times higher after dosing with thimerosal in comparison to methyl mercury. However, you fail to mention that levels of organic mercury, which are of greater concern, are approximately 3-fold greater following dosing with methylmercury and the half-life of organic mercury in the brain is much shorter following dosing with thimerosal than with methylmercury (14 versus 58 days). We presume that your statement "that the 'inorganic form' of mercury that is present in the brain has a half-life of more than 20 years" (page P-290 of your petition) is based on the study by Sugita, et al. (1978) (your footnote 263). As discussed above, (see Section 1.B.5) Sugita based his estimates of the half-life of mercury on the tissue concentration of total mercury rather than distinguishing between organic and inorganic forms. Thus, Sugita does not support your conclusion that inorganic forms of mercury in the brain have a half-life of more than 20 years

Toxicity is a dosing phenomenon and the data currently available indicate that the degree of exposure derived from marketed drug products is not of a sufficient level to induce toxicities. Further, clinical experience with these products has provided no evidence of significantly toxicity in humans.

In our 2006 response, FDA referenced chronic toxicity studies of PMA in rats and discussed the EPA NOEL level for PMA to estimate risk of PMA in nasal solutions and sprays as well as in ophthalmic ointments. You agreed that the most conservative NOEL value should be used and acknowledged how FDA obtained the NOEL value for PMA from the referenced two-year rat study (Fitzhugh, et al. 1950) (page P-292 of your petition). However, you now argue that the EPA reports an ADI value that should be used in humans as 0.08 μg/kg/day, a value that is two orders of magnitude lower than the acceptable level chosen by the FDA. You suggest that FDA should have used the EPA value and not the "8.4 μg/kg/day PMA" which is studied in rats. (Id.)

FDA was aware of the EPA determination of an ADI when its original recommendations were made. The EPA Integrated Risk Information System (IRIS) identified a NOEL of 8.4 μg/kg/day for the rat study conducted by Fitzhugh, et al. (1950). IRIS also states that the ADI of 0.08 μg/kg/day or 6 0 μg/day for a 70 kg person was derived by dividing the NOEL by an uncertainty factor of 100 to account for species extrapolation and differences in human sensitivity. FDA identified the same NOEL value from chronic rat study as did the EPA. In contrast to the EPA approach, FDA compared the NOEL value with an estimated maximum daily human exposure and determined that there was a safety margin of approximately 10-fold. This margin of safety is considered to be acceptable given the benefit provided by pharmaceutical products. It is important to note that the EPA regulates exposures from various environmental sources and

considers these exposures in light of the general population, which receives no direct benefit from the exposure.

In your discussion of dosages of nasal solutions or sprays containing PMA, you agreed with FDA's calculated human dose of PMA but argued that the calculated daily exposure exceeds the EPA ADI by more than a factor of 10 (page P-293 of your petition). You conclude, therefore, that the data established that the current use of PMA as a preservative in nasal products cannot be presumed to be safe and the FDA should have required, and should now require manufacturers to prove safety in scientifically sound and appropriate toxicology test, including reproductive toxicity tests of the formulation in, at a minimum, a mammalian species (preferably a primate) having comparable mercury sensitivity to that observed in humans, with a dose 100 times the maximum dose allowed on the label to allow for a more valid extrapolation than that with rats, which is known to be less than accurate in many cases." (page P-293 of your petition). You further state that it is inappropriate to assume that intranasal exposure in humans is comparable to dietary exposures in rats because the exposure pathway provides almost direct access to the brain and bypasses the stomach, where significant degradation of PMA should occur, and note that no studies or citations were provided to support the agency's assumption) (page P-294 of your petition).

As stated above, FDA's determination that the maximum anticipated human daily exposure was safe was based on an identified NOEL from a chronic rat study. The determination of safety is further supported by the fact that that the agency's calculated anticipated maximum daily human exposure is a level that is approximately 3 times the recommended labeled use. Thus, a 30-fold safety margin is present based on the recommended labeling.

FDA acknowledges that there are no specific studies to support the assumption that intranasal exposure in humans is comparable to dietary exposure in rats. However, there are also no data suggesting exposure to mercury would be greater in humans via intranasal exposure. Accordingly, it was decided to assume similar exposure levels in evaluating the available information. Another factor taken into consideration was that the NOEL was identified from a 2-year rat study, a duration which essentially encompasses the entire lifetime of this species. The exposure to humans using these nasal products is anticipated to be a much smaller fraction of a person's lifetime.

In our 2006 response, FDA stated that there was no current pharmacokinetic data available to support petitioner's assumption regarding intracranial exposure in humans compared to dietary exposure in rats; however, accumulation of mercury following chronic use was not expected due to the relatively quick clearance of inorganic mercury.

You state that the previously cited studies indicate rapid clearance from blood and urine, and not rapid or complete clearance from the body. You have referenced a study by Sugita, (1978)[41] suggesting that the inorganic mercury generated in the brain has a 20-plus year half-life, indicating slow clearance of tissue bound inorganic mercury. Additionally, you referenced Burbacher, et al. (2005),[42] who noted that, despite a 7 day half-life in blood, the half-life of

[41] Your footnotes 11(b), 118(a), 192, 198, 263, 291, 293, and 341(a).
[42] Your footnote 288.

organic mercury in the brain of developing monkeys was about a month with significant long-term accumulation (> 4 months) of inorganic mercury from the brain's metabolizing organic mercury to inorganic mercury. As stated in Section I.B.5., Sugita, (1978)[43] based his estimate for a half-life of mercury on the tissue concentration of total mercury rather than distinguishing ethylmercury from total mercury. Thus, this reference does not appear to be relevant to the question of the safety of ethylmercury. In addition, there are no data with regard to the effects of inorganic mercury in the brain.

Also, it should be noted that you have cited no data demonstrating that PMA distributes significantly to the brain following intranasal exposure and that, if it does, once converted to inorganic mercury it will share similar clearance properties. More importantly, the overall safety assessment does not change since the initial safety evaluation was based on a lifetime rodent toxicology study that incorporated the effects of potential accumulation of inorganic mercury in the brain. It was previously concluded that an acceptable margin of safety is present between the NOEL identified in the chronic rodent study and the maximum human exposure to PMA through the use of nasal products.

In our 2006 response, FDA stated that "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 to these products at all, or at least to be exposed with medical supervision to help ensure that the exposure is not excessive." You state that you find the Agency's reassurance unconvincing since the exposure level in 6 year olds can easily be greater than 25 times the EPA ADI and developing children have been shown to be more sensitive to being poisoned by mercury than adults (page P-295 of your petition).

Assuming a body weight of 20 kg for a 6 year old child, and using the previously calculate maximum anticipated human exposure estimates described earlier (mercury exposure of 43.34 µg/day), the dose to a child would be 2.17 µg/kg/day. This exposure level is approximately 4-fold lower than the NOEL identified in a chronic rat study. However, the realistic exposure levels for a child are expected to be significantly lower considering that the calculated maximum anticipated human exposure estimates are approximately three times the recommended use on the product label and that the actual use would not be on a daily basis for a chronic period of time. Based on the former factor alone, the expected exposure provides a greater than 10-fold margin of safety in comparison to the chronic study in rats and is considered acceptable.

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 [sic; 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 2-year study in rats provides a 15-fold safety factor compared to the maximum human exposure. Therefore, FDA concludes that the use of PMA in ophthalmic products does not pose a treat to

[43] Your footnotes 11(b), 118(a), 192, 263, 291, 293, and 341(a).

human health and you have agreed with the FDA's dose calculations for ophthalmic products (page P-293 of your petition). However, you suggest that the expected dose exceeds EPA's ADI by a factor of 7 for a 50 kg person and 60 for a 5 kg child. As addressed above, the acceptable safety margins were based on the chronic rat study.

In our 2006 response, FDA stated that the use of Thimerosal in nasal products does not pose a threat to human health. You agree with FDA's calculation of the maximum human daily dose of 0/025 mg/d or 0.0005 mg/kg/d, based on a 50 kg person (page P-308 of your petition). However, you assert that the EPA that the EPA human derived value for methylmercury (0.1 µg/kg/d) based on human consumption studies consumption studies, and not the NOEL from a rat study with thimerosal, should be used as the upper limit for safety for mercury in thimerosal-preserved nasal sprays. The maximum human dose based on FDA's calculations exceeds the EPA value by 5-fold for a 50 kg adult and 50-fold for a 5 kg child. You note that PMA is also used in nasal sprays, and for humans, EPA established a daily guideline dose of 0.08 µg mercury/kg/day. Using the daily guideline dose of 0.08 µg mercury/kg/day, the maximum human dose based on FDA's calculations exceeds the EPA value by approximately 6-fold for a 50 kg adult and 60-fold for a 5 kg child.

We do not agree with your calculation of the maximum acceptable human dose. The safety evaluation of thimerosal for nasal products was based on toxicity studies conducted in rats.[44] These studies were conducted under a contract by Division of Biological Standards (now Center for Biologics Evaluation and Research, FDA) and were conducted in three stages: 1) acute toxicity; 2) 4-week injection of five dose levels to determine a maximum tolerated dose (MTD); and 3) chronic toxicity and carcinogenicity testing. The MTD for thimerosal after 4 weeks of injection was 5.0 mg/kg and a high does of 1.0 mg/kg was established for the chronic study. After one year of twice weekly subcutaneous dosing at levels of 0.03, 0.1, 0.3, and 1.0 mg/kg, there was a dose related increase in the incidence of bronchopneumonia, described by the investigators as "slight," that did not affect mortality. Thus, the NOEL was at least 1.0 mg/kg for rats under the conditions of this study. Based on this data, the investigators concluded that thimerosal was a reasonably safe preservative for biological products. This study was considered adequate to use for comparison to human exposure and was used for the risk estimate of thimerosal in nasal products as described in FDA's 2006 response.

We acknowledge that the EPA has set a reference dose of 0.1 µg/kg/day for methylmercury. However, we note that the EPA IRIS website did not confirm your claim of a daily guideline dose of 0.08 µg mercury/kg/day (page P-308 of your petition). Moreover, the use of toxicity data specifically derived from studies with thimerosal as described in FDA's previous response are considered to be most appropriate and the safety calculations presented previously for adults and children are considered to be valid. Therefore, we again conclude that the NOEL of 1 mg/kg identified in a chronic rat study provides a safety margin of approximately 2000 times the estimated exposure to adults and approximately 110 times the estimated exposure in infants.

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[44] Mason, M., et al., Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines. Clinical Toxicology, 1971;4(2):185-204; Kirschstein, R., Toxicology and Carcinogenicity of Preservatives Used in the Preparation of Biological Products. International Symposium on Preservatives in Biological Products, San Francisco 1973. Develop. Biol, Standard, 1974; 24:203-212. (S. Karger, BasellAluenclienlParislLoIlsonlNew York/Syd1ley 1974).

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 products. The recommended usage for these products is 1 drop in each eye four times a day. As an exposure estimate, an extreme usage of these products would be 2 drops in each eye every hour for 24 hours. At a volume of 50 µl (sic; µL) per drop, the total daily exposure to mercury would be 0.35 mg/day or 5 µg/kg/day in a 50-kg person. The NOEL of 1.0 mg/kg/day for chronically administered thimerosal in rats (equivalent to 1,000 µg/kg/day) is over 200 times the estimated exposure to humans based on an exaggerated dose regimen via the ophthalmic route. Therefore, the use of thimerosal in ophthalmic products does not pose a threat to human health.

You state that the level of thimerosal in "ear drops" products is more than sufficient to mercury poison a child and that the maximum exposure levels in all cases, including otic products, exceed the EPA's guidelines that were based on the consumption of methylmercury in fish.
Furthermore, you deem the EPA's human based standard a better estimate than the putative NOEL for thimerosal in studies of rats (pages P-309-P-310 of your petition). In our 2006 response, FDA stated that 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 nasal products (0.002%). As delineated in our 2006 response, and also summarized above, 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 and is approximately 110 times the estimated exposure in infants using the same exaggerated dosing regimen. Furthermore, the NOEL of 1.0 mg/kg/day for chronically administered thimerosal in rats is over 200 times the estimated exposure to humans based on an exaggerated dose regimen via the ophthalmic route. Based on these assumptions for the nasal and ophthalmic products, there was no exposure estimation conducted for the otic products. We continue to maintain that the use of thimerosal in otic products is considered not to pose a threat to human health and we consider the previous safety assessment cited in FDA's 2006 response to be valid because the data are derived from studies conducted with thimerosal rather than based on consumption of methylmercury in fish.

3. Influenza vaccine

a. Recommendations to immunize children 6-59 months of age and pregnant women with influenza vaccine

As the data referenced below show (see 3.b. and 3.c.), children less than 5 years of age and pregnant women are at increased risk from influenza-related morbidity and mortality. Thus, the Advisory Committee for Immunization Practices (ACIP) recommends vaccination of these groups. The recommendation to immunize children with influenza vaccine is based on evidence that children 6-23 months of age are at increased risk of influenza-associated hospitalization and that those 24-59 months of age are at increased risk of influenza-related visits to clinics and emergency departments.[45] There is currently one inactivated influenza

[45] Izurieta, H., et al., Influenza and the rates of hospitalization for respiratory disease among infants and young children, New Engl J. Med, 2000;342 232-9; Neuzil, KM., et al., The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children New Engl. J. Med. 2000; 342 225-32; Poehling, K., et al., The Unrecognized Burden of Influenza in Young Children N. Engl. J. Med 2006;355 31-40.

vaccine (Fluzone) that is licensed in the US to immunize children as young as 6 months of age to protect against influenza. A second inactivated influenza vaccine, Fluvirin, is approved for persons 4 years of age and older. In addition, FluMist, a live attenuated influenza vaccine that contains no thimerosal, is approved for immunization of children 2 years and older.

In the U.S., currently licensed influenza vaccines are not labeled for use during pregnancy. However, for pregnant women at risk of serious consequences from influenza, the ACIP recommends the administration of inactivated influenza vaccine. These are recommendations based on the desire to protect pregnant women during a time of imminent disease exposure, The general approach taken by the ACIP is that the benefit of vaccination among pregnant women usually outweighs the risk for potential adverse effects in the mother or developing offspring when a) the risk for disease exposure is high, b) infection poses a special risk to mother and fetus, and c) the vaccine is unlikely to cause harm[46] These are recommendations and are not FDA-approved indications for use of vaccines during pregnancy.

b. Data regarding morbidity and mortality of influenza in children

You state that "[b]ased 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" and you have submitted Table 2 in your petition entitled "Number of influenza deaths per year in children" to support this statement. We note that the table included data up to the year 2001. You argue that "[f]rom this data, *even if effective*, the influenza vaccination of all children 6 months to 23 months of age is *obviously* not cost justified. (pages P-286-P-287 of your petition) (emphasis in original).

We note that beginning in October 1, 2004, CDC added influenza-associated pediatric mortality (i.e., among persons aged < 18 years) to the list of conditions voluntarily reportable to the National Notifiable Diseases Surveillance System (NNDSS).[47] Moreover, we cite from the Pediatric Influenza Mortality reporting system http://www.cdc.gov/flu/weekly/fluactivity.htm that provides a summary of influenza-associated pediatric mortality occurring between October 1, 2006 – May 19, 2007:

> [a]s of August 6, 2007, among persons aged < 18 years, a total of 68 deaths associated with influenza infections occurring during October 1, 2006 – May 19, 2007, were reported to CDC. These deaths were reported from 26 states (Alabama, Alaska, Arizona, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Kansas, Louisiana, Minnesota, North Carolina, Nebraska, Nevada, New Mexico, New York, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Virginia, Washington, and Wisconsin), Chicago, and New York City. All patient had laboratory-confirmed influenza virus infection. Age-specific information was available on all 68 cases. Of these, 10 were <6 months, 10 were 6-23 months, 9 were 2-4 years, and 39 were 5-17 years of age. Of the 63 cases for which the

[46] www.cdc.gov/vaccines/pubs/preg-guide.htm#flu1.
[47] See www.cste.org/ps/2004pdf/04-ID-04-final.pdf and MMWR Weekly October 15, 2004/53(40); 951-952.

influenza virus type was known, 47 were influenza A and 16 were influenza B viruses. Of the 53 cases 6 months of age and older for whom the vaccination status was known, 50 (94%) were not vaccinated against influenza.

Laboratory-confirmed influenza-associated pediatric hospitalizations are also monitored in two population-based surveillance networks, namely the Emerging Infections Program (EIP) and the New Vaccine Surveillance Network (NVSN). During November 4, 2007- March 29, 2008, the preliminary laboratory-confirmed influenza-associated hospitalization rate reported by the NVSN for children 0-4 years old was 5.62 per 10,000. During September 30, 2007-March 29, 2008, the preliminary laboratory-confirmed influenza-associated hospitalization rate reported by the EIP for children 0-17 years old was 1.32 per 10,000. For children aged 0-4 years and 5-17 years, the rate was 3.47 per 10,000 and 0.45 per 10,000, respectively.

In addition, a recent publication by Bhat, et al. (2005)[48] that described the results of enhanced surveillance of deaths associated with laboratory-confirmed influenza in children during the 2003-2004 influenza season found 153 deaths among children during the 2003-2004 period. The median age of the children was three years, 61 (40%) were younger than 2 years of age and 96of them (63%) were younger than five years old. Information about influenza-vaccination status was available for 11 of the 135 children at least 6 months of age and only 18 children (16%) had received at least one dose during the 2003-2004 season. Only 8 of the 18 children who had received at least one dose during the 2003-2004 season had documentation of full influenza vaccination during that season. In 2007, the ACIP recommend~~s~~ed that children six months to eight-plus years of age receive 2 doses of influenza vaccine during the first year of vaccination and one dose in each subsequent season to afford protection.

Together, these data further demonstrate that influenza-associated mortality is significant in very young children. Furthermore, the data suggest that a substantial proportion of influenza-associated deaths in young children may be prevented using adequate influenza vaccine coverage.

c. Data regarding morbidity and mortality of influenza in pregnant women

Historically, pregnant women have a substantial morbidity and mortality associated with influenza infection.[49] Epidemiological studies as well as case reports of influenza complications associated with pregnancy have been published and report more serious complications and mortality during the later stages of pregnancy.[50] In addition, studies have shown that during

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[48] Bhat, N., et al., Influenza-Associated Deaths among Children in the United States, 2003–2004. N. Engl. J. Med. 2005;353;24 2559-67.

[49] Harris, JW., Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. JAMA 1919;72 978-80; Widelock, D., Csizmas, L. Klein, S., Influenza, pregnancy, and fetal outcome. Public Health Rep 1963;78:1-11; Freeman, DW., Barno, A., Death from Asian influenza associated with pregnancy. Am. J. Obstet. Gynecol. 1959:78 1172-5; Greenberg, H., et al., Maternal mortality in the epidemic of asian influenza. New York City, 1957, Am. J. Obestet. Gynecol. 1958;76 897-902.

[50] Kort BA, Cefalo RC, Baker VV., Fatal influenza A in pregnancy. Am J Perinatol 1986;3:179-82; Irving, WL., et al., Influenza virus infection in the second and third trimesters of pregnancy: a clinical and

Influenza season, hospital admissions and physicians visits as a result of respiratory illness are increased in pregnant women.[51]

These data demonstrate that pregnant women are at increased risk from influenza-related mortality and morbidity.

d. Effectiveness and safety of influenza vaccine in 6-23 month old children

The effectiveness of influenza vaccines depends on the age and immunocompetence of the vaccine recipient, he degree of similarity ("match") between the circulating wild-type influenza viruses in a given season and the vaccine strain, influenza activity in a given season, vaccination coverage, and the clinical outcome measured. A number of studies have demonstrated vaccine efficacy among children aged ≥ 6 months, with varying efficacy estimates. For example, a randomized trial during five influenza seasons (1985-1990) in the United States among children 1-15 years of age, annual vaccination reduced laboratory-confirmed influenza A substantially.[52] In addition, a retrospective study conducted by Rizwoller, et al. (among approximately 30,000 children aged 6 months to 8 years during an influenza season (2003-2004) showed that, despite a suboptimal match between the influenza and predominant circulating strains, influenza vaccination provided substantial protection to fully vaccinated children. In this study, vaccine effectiveness in fully vaccinated children was 51% against medically attended, clinically diagnosed pneumonia or influenza (i.e., no laboratory confirmation of influenza), and was 49% among approximately 5,000 children aged 6 to 23 months. This appears to be the largest study evaluating the effectiveness of influenza vaccine in children 6 to 23 months of age (n-5,129).[53] A retrospective study of similar size conducted during the same influenza season in Denver estimated the clinical effectiveness of 2 TIV to be 87% in healthy children aged 6 to 21 months against pneumonia or influenza-related office visits.[54] Data from a large population based study, in which a total of 45,356 children aged 6 months to 23 months received 69,391 trivalent inactivated influenza vaccinations in the Vaccine Safety Datalink cohort between 2001-2003, supported the safety of trivalent inactivated influenza vaccine in this age group.[55]

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seroepidemiological study. BJOG 2000;107 1282-9; Nuezil, KM., et al., Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148 1094-102.

[51] Cox, S., et al., Hospitalizations with respiratory illness among pregnant women during the influenza season. Obstet Gyn 2006;107 1315-22; Dodds, L., et al., Impact of influenza exposure on rates of hospital admissions and physicians visits because of respiratory illness among pregnant women. CMAJ 2007;176 463-8.

[52] Neuzil, KM., Dupont, WD., Wright, PF., Edwards, KM., Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J 2001;20 733-40

[53] Rizwoller DP, et al., Effectiveness of the 2003- 04 influenza vaccine among children 6 months to 8 years of age with 1 vs. 2 doses. Pediatrics 2005;116:153-9.

[54] Allison MA, et al., Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003--2004 season. J Pediatr 2006;149:755-62.

[55] Hambridge, S., et al., Safety of Trivalent Inactivated Influenza Vaccine in Children 6 to 23 Months Old. JAMA 2006;296:1990-1997.

e. Immunogenicity, effectiveness and safety of influenza vaccine in pregnant women

Although most studies of influenza efficacy among pregnant women have not included specific outcomes such as laboratory-confirmed influenza, pregnant women have measurable concentrations of anti-influenza antibodies after vaccination.[56] In addition, passive transfer of anti-influenza antibodies that might provide protection from mothers to neonates has been reported. For example, Reuman, et al. (1087) showed that passive maternal antibody to influenza vaccine strains delayed the onset and decreased the severity of influenza disease in mother/infant pairs with influenza.[57] Recent data derived from a prospective, controlled, blinded, randomized trial in 340 pregnant women showed that the immunization of pregnant mothers with inactivated influenza vaccine had significant clinical effectiveness, reducing laboratory-confirmed influenza by 63% in infants less than 6 months of age. In addition, immunization with inactivated influenza vaccine was effective against other clinical outcomes in these infants, including a reduction of 29% in the rate of respirator disease with fever. Moreover, in pregnant mothers who received inactivated influenza vaccine there was a reduction in the rate of respiratory illness with fever of 36% (Zaman et al. 2008)[58]. These data underscore the immunization of pregnant women with inactivated influenza vaccine can benefit both mothers and infants. Munoz, et al. (2005) performed a retrospective electronic database search of 5 influenza seasons and compared outcomes in pregnancy between a cohort of healthy women who received influenza vaccine and a control group of health unvaccinated women matched by age, month of delivery, and medical insurance. Influenza vaccine that was administered in the second and third trimester of gestation was safe in this population.[59] In addition, in the 1950s and '60s, the Collaborative Perinatal Project was carried out in the U.S. and over 50,000 immunized pregnant mothers and their offspring were followed for 7 years. No significant increases in adverse reactions in the mothers or their related or potentially related to vaccines were observed. Over 2000 doses of trivalent inactivated influenza vaccine were administered. Infants born to 650 women in the group who had received trivalent inactivated influenza vaccine did not show malformations associated with influenza vaccine.[60]

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[56] England, JA et al., Maternal Immunization with Influenza or Tetanus Toxoid Vaccine for Passive Antibody Protection in Young Infants. J Infect Dis, 168:647-56(1993); Puck JM, et al., Protection of Infants from Infection with Influenza A virus by Transplacentally Acquired Antibody. J Infect Dis, 142:844-9 (1980); Reuman PD, Ayoub EM, Small PA, Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. Pediatr Infect Dis J, 6:398-403 (1987).

[57] England, JA et al., Maternal Immunization with Influenza or Tetanus Toxoid Vaccine for Passive Antibody Protection in Young Infants. J Infect Dis, 168:647-56(1993); Puck JM, et al., Protection of Infants from Infection with Influenza A virus by Transplacentally Acquired Antibody. J Infect Dis, 142:844-9 (1980); Reuman PD, Ayoub EM, Small PA, Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. Pediatr Infect Dis J, 1987;6:398-403.

[58] Zaman, K, et al., Effectiveness of Maternal Influenza Immunization in Mothers and Infants, N. Eng. J. Med. 2008;359:1555-1564.

[59] Munoz, FM, et al., Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol, 2005:192:1098-106.

[60] Heinonen OP, Slone D, Shapiro S. Immunizing Agents, in: Kaufman DW, editor. Birth Defects and Drugs in Pregnancy. Littleton (MA):Publishing Sciences Group; 1977; 314-21; Heinonen OP, et al., Immunization During Pregnancy Against Poliomyelitis and Influenza in Relation to Childhood Malignancy. Intern J Epidemiol, 1973;2:229-35.

Together, data discussed above (3. b., c., d., and e.) demonstrate that children and pregnant women are at increased risk from influenza-related mortality and morbidity and provide evidence that immunization with influenza vaccine can provide protective effects.

f. The agency's response to petitioner's [sic; petitioners'] assertions that influenza vaccine is not effective

You assert that you have shown that influenza vaccines are ineffective[61] and have cited a number of references[62] to support your statement. You claim that Cannell, et al. (2006), have established that daily doses of Vitamin D during the "flu" season are effective in preventing a person from contracting human influenza (your footnote 213). We have reviewed the article that you submitted and find that it does not support such a conclusion. The authors state that the hypothesis that Vitamin D might be effective in preventing seasonal respiratory infections "must be properly addressed through properly conducted clinical trials" and that "it is premature to recommend Vitamin D for either the prevention or treatment of viral respiratory infections." You cited studies by Jefferson, et al. (2005) and Maeda, et al. (2004) to support your statement that inactivated influenza vaccine is not effective in 6-23 month old children (your footnotes 282 and 283). Maeda, et al. (2004) studied an influenza vaccine licensed in Japan and not in the U.S. and given by a different route of administration than vaccines used in the U.S. Thus, the findings are of little relevance with regard to the effectiveness of U.S. licensed influenza vaccines. Jefferson, et al. (2005) performed a review of published controlled trials evaluating influenza effectiveness in children. The observation made by Jefferson, et al. (2005), namely that inactivated influenza vaccine was "not more efficacious than placebo" in children less than 2 years of age, was based on the results of one study which he misinterpreted. That study was a study conducted by Hoberman, et al. (2003) evaluating whether inactivated trivalent influenza vaccine is effective in reducing the occurrence of acute otitis media.[63] The results showed that the influenza vaccine was not effective against otitis media. However, in that study the evaluation of the efficacy against culture proven influenza in young children was a secondary outcome. Notably, during the first year of the study, when influenza was epidemic in the community, vaccine effectiveness against influenza in children 6 to 12 months, 13 to 18 months and 19 to 24 months were 63%, 66% and 69%, respectively. During the second year of the study, influenza occurred infrequently, and thus, it was not possible to obtain efficacy estimates for the vaccine.

g. Availability of thimerosal-free influenza vaccines

FDA has approved preservative-free formulations (which contain either no, or only trace amounts of, thimerosal) for 2 licensed inactivated influenza vaccines that are indicated for children. These are sanofi pasteur's Fluzone vaccine, which is approved for use in children as young as 6 months of age, and Novartis' Fluvirin vaccine, which is approved for persons 4 years of age and older. These influenza vaccines continue to be marketed in both preservative-free and thimerosal-preservative-containing formulations. In addition, FluMist, the live attenuated influenza vaccine (FluMist, manufactured by MedImmune), contains no thimerosal, and was

[61] Pages P-179, P-182, P-252, P-254, p-285, P-286 and P-287 of your petition.
[62] Your footnotes 211, 212, 214, 215, 282, and 283.
[63] Hoberman, A, et al., Effectiveness of Inactivated Influenza Vaccine in Preventing Otitis Media in Young Children A Randomized Controlled Trial. JAMA 2003;290 1608-16.

And was recently approved to extend the indication to as young as 2 year olds. In addition, GlaxoSmithKline's (GSK) inactivated influenza vaccine, Fluarix, has no thimerosal-preservative but contains trace amounts of thimerosal (≤ 1ug [sic; µg] mercury/0.5 ml [sic; mL]) and is approved for persons 18 years of age and older. In the fall of 2007, FDA licensed Afluria, an inactivated influenza vaccine indicated for persons 18 years of age and older, which is also available in thimerosal preservative-free formulations.

Formulations of influenza vaccine containing no thimerosal or only trace amounts of it are currently available to pediatric populations and pregnant women. Based on an estimated annual birth cohort in the U.S. of 4 million, there would be approximately 20 million infants and children between the ages of 6-59 months, most of whom would need 2 doses each. However, the current amount of thimerosal preservative-free vaccine available is below the amount needed for this age group, let alone the approximately 180 million Americans, including pregnant women, for whom the vaccine is recommended.

However, several manufacturers currently are pursuing pediatric indications with thimerosal preservative-free formulations of influenza vaccines. Moreover, FDA is working closely with influenza vaccine manufacturers as they pursue novel technologies that would obviate the need for a preservative in multidose vials as required by regulation (21 CFR 610.15).

You state that FDA's decision to license thimerosal-containing influenza vaccines is inconsistent with its desire to remove mercury from vaccines. As discussed above, even though some influenza vaccines still contain thimerosal preservative, FDA continues its discussions with manufacturers about increasing their capacity to produce influenza vaccines without thimerosal to eventually supply the entire U.S. market with thimerosal-free influenza vaccine. However, FDA recognizes that the goal of reducing mercury exposure from vaccines must be balanced against the goal of having enough vaccine available. If FDA were to revoke the licenses for all thimerosal-containing influenza vaccines, many people would be in serious danger from influenza that this vaccine can prevent.

II. THE STUDIES CITED AND RELATED ARGUMENTS DO NOT SUPPORT PETITIONER'S CONTENTIONS THAT THIMEROSAL AS DOSES USED IN VACCINES AND OTHER DRUG PRODUCTS PRESENTS SAFETY CONCERNS

The fundamental issue underlying your citizen petition is that thimerosal and other mercury-based compounds in pharmaceuticals cause mercury poisoning (page P-318 of your petition), that the science demonstrates that mercury is unsafe in vaccines and medical products and that FDA has not proven mercury derivatives contained in biological or drug products are "sufficiently nontoxic." You have provided numerous reference describing studies evaluating the effects of thimerosal and other mercury-containing compounds and/or mercury derivatives on in vitro cell cultures and tissue cultures,[64] plants (e.g., your footnote 51) and animals,[65] and you have cited literature on the effects of mercury in animals and humans after exposures to mercury in animals and humans after exposure to mercury through consumption of mercury-contaminated food[66] and after accidental exposure (e.g., your footnotes

[64] E.g., your footnotes 9(a), 9(b), 10, 28, 29, 30, 31, 83, 86, 91, 93, 99, 1000, 101, 102, and 103.
[65] E.g., your footnotes 52, 53, 56, 58, 59, 63, 76, 77, 78, 80, 82, and 82.
[66] E.g., your footnotes 54, 55, 62, 64, 65(a), (b), and (c), 66, 67(a), 67(b), 68. 69, 70, 71, 72, 73(a) and (b), and 75.

64, 79, 104). You also cite literature describing use of thimerosal and other mercury-containing compounds and/or derivatives in the treatment of infectious diseases and their use in the blood program in World Wars I and II,[67] as antiseptics,[68] use as pesticides (e.g., your footnote 57), use as fungicides (e.g., your footnote 61), use as preservatives in anti-lymphocyte globulin or gammaglobulin (e.g., your footnotes87,88, 90, 109), or use as a preservative in vaccines where it caused, in some cases, hypersensitivity reactions (e.g., your footnote 98). We also evaluated the 119 additional references listed on pages P-54 through P-61 of your petition describing effects of mercurial compounds on cell and tissue cultures, animal models, plants, insects, and humans. We note that most of the articles cited on pages P-54 through P-61 of your petition describing studies in humans involve mercury exposure as a result of food consumption, exposure of dental workers to elemental forms of mercury and other environmental exposures; however, they did not address mercury exposure as a result of thimerosal preservative in vaccines.

It is well understood that various forms of mercury can exert neurotoxic and other adverse effects when administered under certain doses and conditions to cells, animals and humans. However, the data you cite are not directly relevant to the concerns over potential risks from low doses of ethylmercury in vaccines, and the data do not establish "proof of toxicity" or "proof of harm" of thimerosal in vaccines at the concentrations found in **thimerosal-containing vaccines** or **other drug products under the conditions that these products are administered, indicated and recommended.**

You cited a study by Paran, et al. (2005) (your footnotes 8 and 285) who evaluated the effects of thimerosal on neurotrophin signaling and survival in an in vitro culture system using a human neuroblastoma cell line. Direct exposure of these cells to thimerosal at concentrations between 1nM-10 uM [sic; µM] caused concentration-dependent inhibition of nerve growth factor signaling pathways and cytotoxicity. You conclude that, based on this article, the "…the current established limit for lethal toxicity (apoptosis) of Thimerosal to human neurons is < 0.001 ug [sic; µg] of thimerosal (< 0.0005 ug [sic; µg] of mercury) per ml of growing mesh" page P-236 of your petition). You state 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-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 " (page P-236 of your petition)(portions of the emphasis omitted). As stated in our 2006 response, 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 because uptake, metabolism, and excretion are not taken into consideration. In other words, it is not at all established that the dose levels of thimerosal, and its metabolites studied in this in vitro system, model the actual cellular exposure in the context of the human body.

Thus, the real question is whether thimerosal in "low" or "trace" amounts, or as a preservative in vaccines that are recommended for children and/or adults (e.g., influenza vaccines) actually causes harm to the recipient. To address this, FDA, in 1999, conducted a review of thimerosal in childhood vaccines and found "no evidence of harm from the use of thimerosal as a **vaccine preservative**,

[67] E.g., your footnotes 19, 20, 32, 33, 34, 37, 41, 92, 95, and 97.
[68] E.g., your footnotes 42, 43, 44, 84, 105, and 106.

other than local hypersensitivity reactions" (Ball, et al. (2001), your footnote 235). The Institute of Medicine's Immunization Safety Review Committee reached a similar conclusion in 2001, based on the available data, and again in 2004, after reviewing epidemiological studies performed after its 2001.[69] Since then, additional studies were published confirming these findings.[70] Despite the lack of evidence for any safety concern arising form thimerosal preservative in vaccines, FDA supports the goal of reducing human exposure to mercury wherever possible. Since 2001, no new vaccine licensed by FDA for use in children has contained thimerosal as a preservative and all vaccines routinely recommended by CDC for children under six years of age have been thimerosal-free, or contain only trace amounts, except for some formulations of influenza vaccine. Similarly, adult exposure to mercury from vaccines has been reduced in recent years.

In addition, all licensed plasma derivative products, with the exception of the antivenoms [sic; antivenins] noted below, are thimerosal-free, as are all immune globulin preparations, including hepatitis B immune globulin and Rho(D) immune globulin. (see Section I.D.1). Four snake and spider antivenoms [sic; antivenins] that contain ethylmercury preservatives remain on the market today, and must remain until mercury-free substitutes are available. Mercury continues to be used in approximately 40 over-the-counter nasal solutions or sprays and five ophthalmic ointment products. The mercury exposure from those products poses no known human health threats when used as described in product labeling (Section I.D.2).

III. PETITIONERS' LEGAL ARGUMENTS LACK MERIT

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

1. The products at issue have been proven safe under the applicable statutory and regulatory requirements

Your primary argument appears to be that FDA abused its discretion by licensing and/or approving thimerosal-preserved products that have not been proven to be safe to the extent required by 21 CFR 610.15(a). You assert that "a drug must meet all safety requirements before … FDA … can use its discretion to determine 'safety' by weighing the drugs potential benefits against its known risks." (page P-217 of your petition). In support of your argument, you cite Berkovitz v. United States, 486 U.S. 531 (1988), a United States Supreme Court decision arising under the Federal Tort Claims Act, 28 U.S.C. § 2680(a) (FTCA).

In Berkovitz, the Supreme Court held that the discretionary exemption of the FTCA did not bar a lawsuit against the government in which the plaintiff alleged that the government had failed to comply with the regulatory standards governing the licensing of vaccines.[71] The discretionary function of the FTCA bars claims against the government "based upon

The exercise or performance or the failure to exercise or perform a discretionary function or duty on the part of a federal agency or an employee of the government, whether or not the discretion

[69] Our footnote 12 above.
[70] Fombonne, et al. (2006), our footnote 14, and Thompson, et al. (2007) our footnote 17.
[71] 486 U.S. at 544.

involved be abused." (28 U.S.C. § 2680(a). According to the Supreme Court, what matters in determining whether or not the exception applies is whether the conduct involves an element of judgment or choice by the government, and it is the kind of judgment that involves considerations of social, economic, or policy considerations. Berkovitz, 486 U.S. at 536. When conduct involves the permissible exercise of policy judgment, in this case scientific judgment, it is protected by the discretionary function exception. Conversely, the discretionary function does not apply "when a federal statute, regulation, or policy specifically prescribes a course of action for an employee to follow." Berkovitz, 486 U.S. at 536.

Berkovitz does not, however, support your assertion that 21 CFR 610.15(a) "sets a minimum 'proof of safety' requirement for preservatives in biological products which implicitly applies to all preserved drug products" (page P-217 of your petition), or your assertion that the products at issue "have not been proven safe to the extent required by 21 CFR 610.15(a)" (page P-215 of your petition). As explained in Section I.A., 21 CFR 620.15(a), states that 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. . . ." However, the regulation does not, by its own terms, require specific kinds of "toxicological proof" or specific "studies" to demonstrate sufficient nontoxicity to all "intended direct and indirect recipients under-worst-case dosing regimen with some appropriate safety factor," as you claim (page P-218 of your petition). Rather it merely articulates the general safety standard by which all ingredients, preservatives, diluents, and adjuvants in biological products are to be scientifically evaluated by the FDA, without specifying any method by which safety must be shown. Furthermore, it does not require specific testing of individual ingredients and does not even define what is meant by "sufficiently nontoxic" or "will not be toxic to the recipient." As a result FDA is given deference in interpreting 21 CFR 610.25(a), and hence, has discretion in determining whether a manufacturer has demonstrated that a preservative is "sufficiently nontoxic" and that the biological product "will not be toxic to the recipient." Therefore, your argument that FDA has abused its discretion is without merit.

3. The claims under 42 U.S.C. § 300aa-27(a)(2) do not articulate any grounds upon which FDA should or could grant the petition

On page P-434 of your petition, you assert that FDA violated "the statutory 'mandate for safer childhood vaccines' set forth in 42 U.S.C. § 300aa-27(a)(2) when it licensed thimerosal-preserved versions of the current Hib, hepatitis B, and DTaP vaccines in the late 1980s and e4arly 1990s. . . ." You also assert that FDA violated § 300aa-27(a)(2) by "adding Thimerosal-preserved and/or containing inactivated influenza vaccines to the recommended childhood vaccination schedule in 2002…." These statements appear to be based on your contention that these vaccines are unsafe and ineffective (page P-434 of your petition) and your assertion that the FDA failed to establish that "reduced levels" of thimerosal in certain childhood vaccines would result in fewer adverse reactions (page P-370 of your petition).

Section 300aa-27(a)(2) authorizes the Secretary of Health and Human Services to use the authorities of the Secretary to promote the development of safer vaccines and implement

comprehensive processes to "reduce the risk of adverse reactions to vaccines." Although the Secretary is charged with promoting safer vaccines and reducing the risks associated with such products, the statute gives him broad discretion to determine how he chooses to fulfill the requirements of § 300aa27(a)(2), and how he chooses to prioritize competing issues relating to vaccine safety.

As previously stated, the Secretary, through authorities delegated to FDA, enforces the statutory and regulatory standards to ensure that vaccines and non-biological drugs are shown to be safe prior to being licensed or approved. Accordingly, there has been no failure on the part of the Secretary to perform any duty under § 300aa27(a)(2).

Based on the scientific reasons discussed above in Sections I and II and the legal reasons set forth in this section, none of the actions and legal remedies you seek against vaccines or other products containing thimerosal is warranted. 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, whether as a preservative or in trace amounts remaining in the final product resulting from the manufacturing process, are safe and no action against those products based on their thimerosal content is appropriate.

IV. AGENCY CONCLUSIONS

For the reasons discussed above, and in our 2006 response to your July 30, 2004 citizen petition, 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 mercury based preservatives have been proven safe under the applicable statutory and regulatory requirements.

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

Sincerely,

'David J. Horowitz's signature'

David J. Horowitz, Esq.
Assistant Commissioner for Policy

cc: Division of Dockets Management
(HFA-305)

Seth Sykes, PhD
Rev. Lisa Karen Sykes and,
3604 Milbrier Place
Richmond, VAA 23233

Mark R. Geier, MD, PhD, FABMG, FACE, President
The Genetic Centers of America
14 Redgate Court
Silver Spring, MD 20905

David A. Geier, BA, President
MedCon, Inc.
14 Redgate Court
Silver Spring, MD 20905

Robert C. Weed
Leslie H. Weed
412 Ponte Vedra Blvd
Ponte Vedra Beach, FL 32082

R. Michael Manning
Bobbie L. Manning
384 High Street
Lockport, NY 14094

Brian S. Hooker, PhD., P.E
Marcia C. Hooker
503 South Young Place
Kennewick, WA 99336