SEP 26 2006

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 CP2004P-0439/CP1

Dear Dr. King and Others:

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

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

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

Here is an outline of our response:

I. LICENSED AND APPROVED PRODUCTS ARE SAFE

A. Exposure to Mercury through Vaccines is Minimal

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

2. Adult exposure to thimerosal through vaccines has been reduced.
B. Exposure to Mercury through other Biologics and Drugs is Minimal

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

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

C. The Few Products that Still Contain Thimerosal are Safe

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

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

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

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

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

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

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

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

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

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

D. The Cited Animal and Human Studies on Thimerosal’s Longevity in the Body do not Study the Consequences of that Exposure
E. The Studies Cited that Recommend Eliminating all Thimerosal from all Products do not Support those Recommendations with Valid Science

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

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

III. PETITIONERS' LEGAL ARGUMENTS LACK MERIT

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

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

IV. AGENCY CONCLUSIONS

DISCUSSION

I. LICENSED AND APPROVED PRODUCTS ARE SAFE

A. Exposure to Mercury through Vaccines is Minimal

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

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

¹ Statement of Karen Midthun, M.D., Director, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services, before the Committee on Government Reform, United States House of Representatives, December 10, 2002.
1. Thimerosal in routinely recommended pediatric vaccines has been removed or reduced.

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

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

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

Prior to the initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first 6 months of life was 187.5 micrograms. With the introduction of thimerosal-
preservative-free formulations of DTaP, hepatitis B, and Hib, the maximum cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life. With the addition in 2004 of influenza vaccine to the recommended vaccines, an infant could receive a thimerosal-containing influenza vaccine at 6 and 7 months of age. This would result in a maximum exposure of 28 micrograms during the first 7 months of life via routine childhood vaccinations. This level is significantly below the Environmental Protection Agency (EPA) calculated exposure guideline for methyl mercury of 65 micrograms during the first 6 months of life for a child in the fifth percentile body weight. (See the enclosure for the table listing the thimerosal content of vaccines routinely recommended for children 6 years of age and younger).

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

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

Nevertheless, FDA supports the development of adult vaccines in thimerosal-free formulations and has encouraged the reduction or removal of thimerosal from all existing vaccines. As with pediatric vaccines, these efforts have succeeded in reducing mercury exposure from thimerosal in vaccines for adults. For example, all hepatitis B vaccines for adolescents and adults are available only in formulations that are free of thimerosal or contain only trace amounts. Tetanus and Diphtheria toxoids (Td) vaccine, which is indicated for children 7 years of age or older and adults, is now also available in thimerosal-free formulations. These changes have been accomplished by reformulating products in single dose vials that do not contain a preservative. In addition, the agency has recently licensed two combination vaccines, composed of tetanus, diphtheria, and pertussis antigens (TdaP), a meningococcal conjugate vaccine, a zoster vaccine, and a human papillomavirus vaccine, none of which contains thimerosal. The thimerosal content of U.S. licensed vaccines, including those indicated for adults, is posted at http://www.fda.gov/cber/vaccine/thimerosal.htm#1.

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

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

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

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

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

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

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

C. The Few Products that Still Contain Thimerosal are Safe

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

Safety is relative, rather than absolute. FDA regulations define safety as “the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation
to the condition of the recipient at the time" (21 CFR § 600.3(p)). If the benefit of
the vaccine or other pharmaceutical product outweighs the risk of the side effects, then FDA
finds the product safe. Applying that relative standard for safety is critical to the public
health because virtually every vaccine -- and every drug, for that matter -- carries the risk
of some side effects. In applying the regulatory standards, FDA must weigh the risk of a
vaccine -- indeed, the risk of any drug -- against its benefits when determining whether
the product is safe.

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

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

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

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

---

2 Thimerosal in Vaccines, Center for Biologics Evaluation and Research. U.S. Food and Drug
3 IOM (Institute of Medicine). Thimerosal-containing vaccines and neurodevelopmental disorders.
methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom). Other studies reported findings of an association. These include two ecological studies (Geier and Geier, 2003a; 2004), three studies using passive reporting data (Geier and Geier, 2003a,b,d) an unpublished study using Vaccine Safety Datalink (VSD) data (Geier and Geier, 2004b,c), and one unpublished uncontrolled study (Blaxill, 2001). However, the studies by Geier and Geier cited above have serious methodological flaws and their analytic methods were nontransparent making their results uninterpretable, and therefore non-contributory with respect to causality . . . . The study by Blaxill is uninformative with respect to causality because of its methodological limitations.

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

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

---

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

a. PMA in nasal and ophthalmic drug products

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

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

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

No prescription nasal solutions or sprays contain PMA; however, PMA is thought to be used in approximately 40 OTC nasal solutions and sprays and five ophthalmic ointment products. As an exposure estimate for nasal solutions and sprays, a 15-milliliter (ml) bottle (0.02 mg/ml) contains 0.3 mg PMA. The recommended usage for these products is 2 to 3 sprays in each nostril not more than every 10 to 12 hours. These products are not generally intended for chronic treatment of rhinitis. However, even people who do not use such sprays chronically may experience rebound nasal mucosal vasodilation and congestion called "rhinitis medicamentosa," which may result in further increased use. A reasonable maximal exposure estimate in humans would be 3 sprays per nostril every 4 hours for a total of 36 actuations per day, 0.07 ml/actuation, resulting in a total daily PMA exposure of 0.05 mg. Because mercury accounts for 86% of PMA by molecular
weight, the daily exposure to mercury from this product approximates 43.34 μg/day or 0.87 μg/kg/day, assuming a 50-kg individual. Thus, the NOEL dose from the two year study in rats provides a 9.7-fold safety factor compared to the maximum human exposure if the maximum recommended dosage as labeled was used chronically, assuming that intranasal exposure in humans is comparable to dietary exposure in rats. There are currently no pharmacokinetic data available to support this assumption; however, accumulation of mercury following chronic use is not expected due to the relatively quick clearance of inorganic mercury. In addition, these products are labeled for adults and children ages 6 years and older. For children under 6, the labeling states to “consult a doctor.” Therefore, children under 6 are less likely to have any exposure to these products at all, or at least to be exposed with medical supervision to help ensure that the exposure is not excessive.

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

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

Thimerosal has been used in pharmaceutical products since the 1930s and is used in ophthalmic and nasal products (Golightly, et al., 1988). It is also found in a few otic products.

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

In a study submitted to an approved new drug application (NDA), chronic toxicity data on 0.001% thimerosal was provided. In that study, rabbits were dosed in the right eye with 2 drops of 0.001% thimerosal 3 times per day for one year and then subjected to full histopathologic evaluation of organs and tissues, including an ophthalmic evaluation that utilized scanning electron microscopy of the corneas. There were no signs of ophthalmic
or systemic toxicity under the conditions of this study. Only one dose level of thimerosal was used, which precludes estimation of a toxicological dose response relationship. Therefore, this study was not further considered for human exposure comparisons.

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

Thimerosal is used in nasal solutions and sprays at concentrations up to 0.002%. Using the dosing regimen previously described (36 actuations/day and 0.07 ml/actuation), the total daily exposure to mercury would be 0.025 mg/day or 0.0005 mg/kg/day, based on a 50-kg person. The NOEL of 1.0 mg/kg/day for chronically administered thimerosal in rats is approximately 2,000 times the estimated exposure to humans based on an exaggerated dose regimen via nasal inhalation. The NOEL is approximately 110 times the estimated exposure in infants (0.009 mg/kg/day, assuming a 3-kg infant) using the same exaggerated dosing regimen. Therefore, we believe that the use of thimerosal in nasal products does not pose a threat to human health.

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

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

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

You state that CoMed’s position on mercury is based on the proven harm that ionic mercury causes at levels of approximately 0.02 µg/ml to growing neurological structures when comparable levels of other ionic heavy metals and ionic aluminum have been shown to cause no observable effects (refer to page P-7 of your petition). You have cited work done by Leong, et al. (2001), in support of this statement. We note that these investigators used an in vitro cell culture system consisting of neuronal cells from a snail to evaluate the effect of chloride salts of mercury, lead, cadmium, and manganese
(1 x 10^{-7} M) on neurite growth cone morphology and behavior. Snail cells were treated with heavy metal solutions by applying pressure injection into the culture media adjacent to neuronal growth cones of the snail. Results showed that mercury ions, when directly infused into in vitro cultures of nerve cells from an invertebrate, inhibit growth of neuronal structures. FDA acknowledges these data; however, the data do not prove that thimerosal in vaccines causes autism in humans, and the investigators did not even attempt to establish that those data are in any way relevant to determining whether any causal relationship exists between thimerosal in vaccines and the development of autism in humans.

Furthermore, on page P-2 in your petition you state that “there is substantial inferential evidence, and some Thimerosal and related-compounds human exposure and animal data that have proven Thimerosal and other mercury-based compounds can cause neurological damage in susceptible individuals at levels of exposure above 0.1 microgram (μg) of mercury per kg.” You state further that, “scientifically sound experimental studies have proven the neurotoxicity of Thimerosal and its metabolites, ethyl mercury and mercureic ion, at ‘mercury’ levels below 0.1 part-in-a-million (0.1 ppm; 0.1 μg per mL or g)” (page P-11 of your petition). You have cited endnote 6 in support of these statements, i.e., studies performed by Baskin, et al. (2003), Makani, et al. (2002), Waly, et al. (2004), Chao, et al. (1984), and Leong, et al. (2001).

These studies were carried out using in vitro cell culture based assays of human cerebral neurons, human T-cell lines, human cervical carcinoma cell lines, and human neuroblastoma cells to evaluate the effects of thimerosal or mercury compounds on cellular processes and pathways, including programmed cell-death (apoptosis), DNA and RNA replication and methylation pathways. Results from these in vitro studies show that mercurial compounds, when directly applied to cell cultures can exert dose-dependent toxic effects. FDA acknowledges these data but concludes that these studies do not prove that thimerosal contributes to the risk of autism for the following reasons: The biochemical and molecular pathways and processes relevant to the expressions of autism are currently not known. Therefore, there is no basis for concluding that the biochemical and molecular pathways studied in these in vitro cell systems are related to the biological processes that underlie the disease of autism. Furthermore, in some of the studies you cite, the effects observed were not specific to mercury compounds, but were also noted with ethanol, lead, and aluminum (e.g., Waly, et al., 2004).

The thrust of your argument appears to be that thimerosal and its metabolites were studied in these in vitro systems using dose levels in the same range, or even lower, than those contained as trace amounts in some of the currently recommended childhood vaccines. FDA acknowledges and values the importance of in vitro systems to elucidate possible mechanisms for drug-induced effects. However, demonstration of a toxic effect of a compound in an in vitro system using isolated cells does not readily translate into potential toxic effects to the human body. The studies you cite assessed the effects of thimerosal and its metabolites on cellular pathways under conditions of in vitro exposure that were extreme in terms of dose regimen, duration, and method of administration. Furthermore, some of the studies required extensive manipulation of the cell system, e.g.,
heavy metal solutions were delivered via pressure injection into snail neuronal cell culture media for a duration of 20 minutes. However, such exposure may not be achieved in vivo, since in the context of a whole organism, it would depend on the uptake (e.g., adsorption), distribution, metabolism, and excretion pathways of the compound. Therefore, the dose levels of thimerosal and its metabolites studied in these in vitro systems may not model the actual cellular levels of exposure in the context of the human body.

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

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

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

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

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

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

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

The studies cited using genetically susceptible rodent models assume that autism is caused by an autoimmune reaction. However, there is no evidence that autistic patients have auto-immune-mediated central nervous system (CNS) damage in the brain (see 2004 IOM report) and there is currently limited understanding of the etiology of autism. Therefore, FDA concludes and agrees with the IOM that even though these rodent models are useful for understanding some of the processes by which exogenous agents may potentially exert adverse effects, the connection between these models and autism is only theoretical (see 2004 IOM report).

FDA wishes to comment on your statement on page P-2, namely that the safety and efficacy of thimerosal, or any other mercury-based compound, be studied in scientifically sound animal studies using appropriate susceptible animal strains. Prior to introducing a novel vaccine formulation into clinical trials, the vaccine is evaluated in nonclinical studies using animal models to assess and detect the potential of the product to cause harm in the animal. Moreover, if the vaccine is indicated for a population that includes females of childbearing potential, vaccine manufacturers are encouraged to perform additional special nonclinical studies in animals to evaluate the potential of the vaccine to harm the developing fetus. However, currently available animal models are limited in terms of their ability to detect rare toxicities, or specific toxicities that may occur in a human subpopulation. To improve on this situation, FDA is working with manufacturers to develop better animal models and assays to measure activity and potential drug-induced toxicity at an early stage in product development.6

Although FDA supports the goal of developing predictive models for nonclinical safety assessments, currently available state-of-the-art test systems would not be able to provide proof of the safety and efficacy of a product formulation as you requested (page P-2 of your petition). FDA acknowledges that it would be useful if nonclinical models were developed that could be used to predict the safety of a biological or drug product in human subjects. However, to date there are no adequate and relevant models that would predict the risk that a vaccine will cause neurological damage, such as autism, in humans. As discussed above, you have suggested using the SJL/J mouse model for such evaluations (page P-5 of your petition). The SJL/J mouse is genetically predisposed to auto-immune diseases, which you hypothesize are an underlying cause of autism. However, to the best of our knowledge, there are currently no data providing evidence of auto-immune mediated central nervous system (CNS) damage in the brain of autistic patients. Therefore, even though these rodent models have value in understanding some of the processes by which exogenous agents may potentially exert adverse effects, we have no basis to extrapolate these findings to neurodevelopmental disorders in humans.

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

On pages P-37 to P-39 of your petition, under your headings “The Link Between Thimerosal And Neurological Disorders” and “Autism Alarm”, you quote reports from California’s Department of Developmental Services, and the Department of Health and Human Services, CDC, and the American Academy of Pediatrics to demonstrate that the incidence of autistic spectrum disorders (ASD) in the United States has increased (endnotes 54, 55, and 56). FDA acknowledges these data; however, the observed increase in autism rates is difficult to interpret. We note that the report of the California Department of Developmental Services stresses that the information in the report “should not be used to draw scientifically valid conclusions about the incidence or prevalence of ASD in California” and “that the number of persons with ASD described . . . do not constitute formal epidemiological measures of incidence or prevalence.” Furthermore, the reports did not address the cause(s) of this increased prevalence and the issues and factors related to the etiology of autism. Notably, none of these reports establishes a causal link between thimerosal and neurological disorders as suggested by you. Moreover, as discussed above in section I.C.2, if it is true that autism rates are increasing, such a fact would contradict, rather than support, your contention that thimerosal in vaccines cause autism, given that the amount of thimerosal that children receive through vaccines has decreased dramatically.

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

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

Holmes, et al. postulated that an impaired mercury excretion might be an important susceptibility factor underlying recent increases in autism. They evaluated mercury concentrations in first baby hair cut samples from 94 autistic children and 45 age- and gender-matched controls. Control samples were collected under the condition that the child received all their childhood vaccinations on schedule, so that they would show comparable postnatal exposure levels. Notably, this study did not attempt to examine the role of childhood vaccine exposure in autism. First baby hair cut samples had been collected by the parents with a mean age at haircut of 17.7 months. Hair mercury levels in autistic children were significantly lower than in controls (0.47 ppm versus 3.63 ppm). Subgroup analysis showed decreased mercury levels in the hair as the autism severity score increased. The lower level of mercury content in baby hair was not caused by less exposure, as the autistic infants were exposed to higher levels of mercury during gestation, through dental amalgams or RhoD immunoglobulin injections in the mother.
As stated by the authors, there are certain limitations to the study, i.e., the study was not of prospective design, recruitment of autistic study subjects was influenced by medical care-seeking behavior, testing facilities were not under the direct control of the investigators, and the population studied may not be representative of the autism population of the whole. Furthermore, it is noted that the "first baby hair cut" hair sample was obtained at a mean age of 17 months and thus, the implications of mercury measurements for prenatal exposures is unclear (see also 2004 IOM report). In addition, infant exposures to other sources of mercury postnatally were not ascertained. The authors' hypothesis -- that children with autism do not "excrete" mercury into the hair and that therefore, mercury burden remains bioactive within the body -- was not supported by data. Neither the authors nor any other studies, to our knowledge, have established that children who have relatively small amounts of mercury in their hair are unable to excrete mercury, and retain unsafe amounts of mercury in their bodies.

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

As pointed out by the IOM (see 2004 IOM report), the range of mercury excreted was 0-59 with a mean of 4.1µg mercury/g creatinine and a standard deviation of 8.6, suggesting that data might be skewed in the direction that most of the children with autism excrete little mercury. Bradstreet, et al. speculate that their results and those of Holmes (see above) might result from a decreased ability of children with autistic spectrum disorders to excrete mercury. The authors conclude that mercury levels measured could "plausibly have resulted from exposure to mercury in routine childhood vaccines in the United States and thimerosal in RhoD immune globulin and other potential environmental sources of mercury may be contributory." According to the hypothesis of the authors (Bradstreet, et al., and Holmes, et al.) thimerosal provides a source of mercury, which a subpopulation of autistic children are unable to process, thus leading to higher mercury burden. It is noteworthy that these papers do not provide any causal link between the thimerosal contained in vaccines and autism; exposure to thimerosal as a result of vaccination was not directly addressed or studied. Given that thimerosal is no longer present in childhood vaccines, other than in trace amounts in a few vaccines and in limited amounts in seasonal influenza vaccines, FDA concludes that even if their unproven hypothesis about autistic children's mercury excretion ability is correct, the contribution of vaccine-related mercury to total mercury burden and toxicity is not significant.
C. Arguments that Thimerosal in the Current Amounts is Insufficient to Qualify as a Preservative or an Adjuvant are Flawed; Thimerosal does Meet the United States Pharmacopeia Standard for a Preservative where it is being used as One, and Thimerosal is not being used as an Adjuvant

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

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

FDA wishes to comment on your statement on page P-12 of your petition that at thimerosal’s current trace levels it does not meet the accepted USP definition of a preservative. We wish to clarify that the trace levels of thimerosal present in single dose vials of vaccines are residual amounts of this preservative added during manufacture to prevent microbial growth. These trace levels do not constitute a preservative and there is no requirement for a preservative in single dose vials. In addition, as to your claim on page P-12 of your petition that manufacturers are using thimerosal improperly as an adjuvant, adjuvants are compounds that are added to vaccines to enhance the immune response to the vaccine antigens. Thimerosal does not serve such function and is not used as an adjuvant in U.S. licensed vaccines indicated for pediatric, adolescent, and adult populations.

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

You state that thimerosal is a neurotoxic compound that should not be permitted in any drug product that is administered to humans or animals unless the manufacturer can prove that the proposed level of the mercury-based compound is safe at 10 times its proposed maximum level and that the medical product cannot safely be used without including this compound or another mercury-containing compound in the formulation (page P-14 of your petition). You have cited articles by Gassert, et al., Redwood, et al., Slikker, et al., Stajich, et al., and Sager, et al., to support this claim (your endnotes 22, 23, 24, 25, and 26).
FDA wishes to comment on the findings of these papers, particularly as they relate to your argument. The purpose of the investigation by Gasset, et al. was to evaluate the effect of thimerosal in rats and rabbits when topically applied to the eye and when systemically administered because of observation that ophthalmic medications produce teratogenic effects. No fetal malformations were observed even when given at concentrations approaching the LD₅₀ (lethal dose at which 50% of the treated animals die) of these compounds, however, there was increased uterine death in both animal species treated with 2% thimerosal. The authors concluded that the accumulation and potential effects of mercury in maternal and fetal tissues, such as kidney, liver, and brain would require further studies.

We wish to emphasize that in this study, animals were dosed with concentrations of mercury that exceeded by a factor of 100 and 1000 the amounts generally present in the currently available childhood vaccines that contain trace thimerosal. Thus, the significance of these findings in the context of trace amounts of thimerosal contained in today’s pediatric vaccines is unclear.

Redwood, et al. (2001) assessed the potential impact of mercury from pediatric vaccines given according to the 1999 infant immunization schedule, by estimating hair mercury concentrations utilizing a one-compartment pharmacokinetic model simulating mercury uptake, distribution and elimination.

FDA wishes to comment on the results of these studies. First, infant hair mercury concentrations were estimated, not actually measured. Second, as also noted by the authors, no attempt was made to factor into the model other sources of exposure, e.g., dietary exposure. Other concerns are whether the model used is appropriate for assessing mercury effects in infants from direct exposure, whether a model developed for methyl mercury ingested with food can be applied to an assessment of ethyl mercury injected with vaccines and finally, which of the two scenarios modeled is more valid, i.e., the “adult excretion model” that assumes mercury excretion rates with a half life of 50 days or the “no excretion model” that assumes no excretion for the first 6 months of life followed by normal adult rates after this point.

Slikker, et al. (2000) discussed thimerosal as a preservative in vaccines in the context of therapeutic agents presenting special challenges to risk assessment because they may present both risk and benefit to human health. He referred to data showing that thimerosal crosses the blood-brain and placental barriers, resulting in accumulation of mercury in the brain. However, he stressed that therapeutic agents represent both risks and benefits to human health and that therefore, there is a need to further study this important ingredient (i.e., thimerosal) with regard to both benefits, and potential associated risk.

Stajich, et al. (1999) measured total mercury levels before and after administration of hepatitis B vaccine (Engerix®) to preterm (n=15) and term (n=5) infants. Even though authors were concerned about increasing the neurologic risk for preterm infants as a
result of mercury exposure, they state that there is no information to suggest a causal link with immunizations. The authors also mentioned that at that time, namely 1999, few alternatives were available to infants born to hepatitis B-infected mothers because a thimerosal-preservative-free hepatitis B vaccine was not yet available. Since then, two hepatitis B vaccines containing either no thimerosal or trace amounts of thimerosal from the manufacturing process have been licensed, and are now the only hepatitis B vaccines available in the United States to all age groups.

Summary results presented by Dr. Polly Sager (2004) at the IOM meeting in February 2004 (cited in your endnote 26) are now published by Burbacher, et al. FDA notes that in this study infant monkeys were administered thimerosal mixed with thimerosal-free vaccines to yield a final concentration of 4, 8, or 20 μg/ml depending on the vaccine and the age of the monkey. The total dose of mercury administered was 20 μg/kg mercury administered on day 0, 7, 14, and 21 days of age. According to the authors, this dose was chosen based on the range of estimated doses received by human infants receiving vaccines during the first 6 months of life. FDA wishes to emphasize that the cumulative amount of mercury from vaccines that an infant less than 6 months of age can now be exposed to is < 3 μg, or approximately 15 μg if a thimerosal-containing influenza vaccine was used at 6 months of age. These levels are significantly lower than the one used in the study by Burbacher, et al. Furthermore, we note that the results of this study do not provide evidence that trace amounts of thimerosal contained in today’s childhood vaccines are linked to neuro-developmental effects.

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


FDA has reviewed the references and notes the following: Nelson and Gottshall (1967) conclude that there are no data to suggest that thimerosal-preserved pertussis vaccines which show a greater toxicity in mice than unpreserved vaccines also have a greater toxicity in man. In addition, we observe that the mice (14-16 g) received doses of 70 μg thimerosal, e.g., 4.6 mg/kg thimerosal, which is approximately 4620-fold the dose of mercury generally contained in today’s childhood vaccines with trace amounts of mercury.

Heyworth, et al. (1979) measured the cytotoxic effects of anti-lymphocytic globulin on peripheral blood mononuclear cells (PBMC, which are white blood cells), tonsil lymphocytes and blood cells in an in vitro system measuring 51Cr release from labeled cells. Because of data in the literature on binding of merthiolate to sulfhydryl (SH) groups of proteins, the authors suggest that if thimerosal binds to horse immunoglobulin,
it may reach a toxic level in the region of lymphoid cells. While data provide further
evidence about the known in vitro cytotoxic effects of mercury, no direct evidence was
provided in this paper that would support the conclusion of the authors.

Kravchenko, et al. (1983) evaluated toxic properties in medical biological preparations by
the degree of cell damage using an in vitro system of an L132 continuous cell line. The
authors conclude that thimerosal has cytotoxic effects on in vitro cell cultures and suggest
that the use of thimerosal in biological preparations, especially those intended for
children, is inadmissible. As stated above (refer to item IIa), FDA acknowledges that
mercurial compounds, when applied directly to in vitro cell systems, can cause dose-
dependent cytotoxic effects; however, these data do not prove that thimerosal causes
harm to the human body.

Winship, et al. (1986) reviewed the use of organic mercury compounds, sources of
exposure, absorption, distribution, biotransformation, excretion, toxicology, and
treatment and states that multi-dose vaccines and allergy-testing extracts containing
0.01% thimerosal may present problems occasionally in practice. Furthermore, the
studies by Farstroem, et al. (1980), Van’t Veen (2001), Cox and Forsyth (1988) and Seal,
et al. (1991), are mainly concerned with hypersensitivity reactions to thimerosal and
primary sensitization to thimerosal. The general conclusion was that overall exposure to
thimerosal should be reduced and in particular the exposure via vaccines and
immunoglobin to children and young adults should be eliminated. FDA must
reemphasize that thimerosal has been removed or significantly reduced from currently
U.S. licensed vaccines indicated for the pediatric, adolescent, as well as the adult
population.

Schumm, et al. (2002) assessed the effects of anthrax vaccination on the long-term health
of U.S. male and female Reserve Component Gulf War veterans. FDA notes that this
author’s interpretations are speculative and no data were presented that would link
mercury contained in the vaccine(s) administered to “adverse long-term outcomes”
experienced by the Gulf War Veterans.

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

You have cited publications by Tryphona, et al., Fagan, et al., and Magos, et al. (endnotes
51, 52, 53) to compare the relative toxicities of ethyl mercury and methyl mercury.
Tryphona, et al. conclude that alkyl mercury compounds, if fed at low concentrations for
long periods, were poisonous to swine. The authors were concerned with public health
implications, especially when meat, liver, etc., of poisoned pigs are consumed by people.
Magos, et al. compared the neurotoxicity and renotoxicity of alkyl mercury compounds in
Porton Wistar rats. FDA acknowledges that alkyl mercury compounds, such as methyl
mercury and ethyl mercury, especially when administered at high doses, are toxic;
however, an extrapolation of the above data to infant exposure at far lower levels of
thimerosal, and neurodevelopmental disorders, is problematic. For example, Tryphona,
et al., was concerned with consumption of parts of pig by humans derived from animals
exposed to certain threshold levels of mercury that may pose health hazards. In addition, in the study by Magos, et al., the cumulative dose administered to rats was 40 mg/kg which is > 13000 times the cumulative dose that an infant less than 6 months of age would be exposed to (<3 μg) through administration of vaccines containing trace amounts of mercury.

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

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

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

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

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

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

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

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

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

Regardless of the scope of the Due Process Clause of the Constitution and the "basic American civil rights and tenants" on which you rely, the facts, even as you allege them, do not amount to the government violating anyone's rights. For example, In re Cincinnati Radiation Litigation involved doctors who were alleged to have subjected indigent cancer patients to increasing levels of radiation to determine what levels that the human body can withstand, even though the doctors knew that the radiation had no therapeutic value to patients. Allegedly the doctors never informed the patients about any
of those facts, but instead told them that the radiation was to treat their cancer. In contrast, here you are not denying that the vaccines and other products have prophylactic or therapeutic value to those who take them. Nor have you provided any evidence to claim that FDA officials have been hired to conduct “uncontrolled involuntary experiments” on people. Nor do you claim that FDA has hidden any facts from those who will use thimerosal-containing products. You simply disagree with the conclusions that FDA draws from those facts. As explained above, however, FDA’s conclusions are based on sound scientific principles.

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

IV. AGENCY CONCLUSIONS

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

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

Sincerely,

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

Enclosure: Table – Thimerosal Content of Vaccines Routinely Recommended for Children 6 Years of Age and Younger (http://www.fda.gov/cber/vaccine/thimerosal.htm).

cc: Division of Dockets Management (HFA-305)

Mark R. Geier, MD, PhD, FABMG, 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

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

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

R. Michael Manning
Bobbie L. Manning
1 Kate Land Court
Getzville, NY 14068

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

James R. Davis
Kelli Ann Davis
748 Three Wood Drive
Fayetteville, NC 28312
Table 1. Thimerosal Content of Vaccines Routinely Recommended for Children 6 Years of Age and Younger - (updated 7/18/2005*)
*Since this update, a biologics license application was approved for Rotavirus Vaccine, Tradename-RotaTeq (Merck), that is thimerosal free and never contained thimerosal.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Tradename (Manufacturer)*</th>
<th>Thimerosal Status Concentration**(Mercury)**</th>
<th>Approval Date for Thimerosal Free or Thimerosal/Preservative Free (Trace Thimerosal)** Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>Infanrix (GSK)</td>
<td>Free</td>
<td>Never contained more than a trace of thimerosal, approval date for thimerosal-free formulation 9/29/00</td>
</tr>
<tr>
<td></td>
<td>Daptacel (AP)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td></td>
<td>Tripedia (AP)</td>
<td>Trace (&lt;0.3 μg Hg/0.5mL dose)</td>
<td>03/07/01</td>
</tr>
<tr>
<td>DTaP-HepB-IPV</td>
<td>Pediarix (GSK)</td>
<td>Trace (&lt;0.0125 μg Hg/0.5mL dose)</td>
<td>Never contained more than a Trace of Thimerosal</td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>Provnar (WL)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td>Inactivated Poliovirus</td>
<td>IPOL (AP)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td>Varicella (chicken pox)</td>
<td>Varivax (M)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td>Mumps, measles, and rubella</td>
<td>M-M-R-II (M)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recombivax HB (M)</td>
<td>Free</td>
<td>08/27/99</td>
</tr>
<tr>
<td></td>
<td>Engerix B (GSK)</td>
<td>Trace (&lt;0.5 μg Hg/0.5mL dose)</td>
<td>03/28/00</td>
</tr>
<tr>
<td>Haemophilus influenzae type b conjugate (Hib)</td>
<td>ActHIB (AP)/OmniHIB (GSK)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------------</td>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>PedvaxHIB (M)</td>
<td>Free</td>
<td>08/99</td>
<td></td>
</tr>
<tr>
<td>HibTITER, single dose (WL)¹</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
<td></td>
</tr>
<tr>
<td>Hib/Hepatitis B combination</td>
<td>Convax (M)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
<tr>
<td>Influenza</td>
<td>Fluzone (AP)</td>
<td>0.01% (12.5 µg/0.25 mL dose, 25 µg/0.5 mL dose)²</td>
<td>12/23/2004</td>
</tr>
<tr>
<td></td>
<td>Fluzone (AP)⁴ (no thimerosal)</td>
<td>Free</td>
<td>09/28/01</td>
</tr>
<tr>
<td></td>
<td>Fluvirin (Chiron/Evans)</td>
<td>0.01% (25 µg/0.5 mL dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvirin (Chiron/Evans) (Preservative Free)</td>
<td>Trace (&lt;1µg Hg/0.5 mL dose)</td>
<td></td>
</tr>
<tr>
<td>Influenza, live</td>
<td>FluMist² (MedImmune)</td>
<td>Free</td>
<td>Never contained Thimerosal</td>
</tr>
</tbody>
</table>

Manufacturer abbreviations:
GSK = GlaxoSmithKline; WL = Wyeth Lederle; AP = Aventis Pasteur; M = Merck.
** Thimerosal is approximately 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of thimerosal contains 50 µg of Hg per 1 mL dose or 25 µg of Hg per 0.5 mL dose.
*** The term "trace" has been taken in this context to mean 1 microgram of mercury per dose or less.
1 HibTITER was also manufactured in thimerosal-preservative containing multidose vials but these were no longer available after 2002.
2 Children 6 months old to less than 3 years of age receive a half-dose of vaccine, i.e., 0.25 mL; children 3 years of age and older receive 0.5 mL.
3 A trace thimerosal containing formulation of Fluzone was approved on 9/14/02 and has been replaced with the formulation without thimerosal.
4 FluMist is not indicated for children less than 5 years of age.