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IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

IN RE: CLAIMS FOR VACCINE INJURIES RESULTING IN AUTISM SPECTRUM DISORDER, OR A SIMILAR NEURODEVELOPMENTAL DISORDER, Various Petitioner(s) v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Autism Master File **REPLY BY AMICUS SMITHKLINE BEECHAM CORPORATION D/B/A GLAXOSMITHKLINE TO PETITIONERS' RESPONSE TO MERCK AND AMICUS CURIAE RE: NON-PARTY DISCOVERY**

SmithKline Beecham Corporation d/b/a GlaxoSmithKline ("SB"), in its capacity as amicus curiae, files this reply to Petitioners' Response to Merck and Amicus Curiae re: Third-Party Discovery ("Petitioners' Response") to show the following:

INTRODUCTION

Petitioners ask the Special Master to take an unprecedented step in issuing a subpoena seeking expansive discovery from a non-party vaccine manufacturer, yet they can point to nothing more than their own expedient interpretation of the Vaccine Court's rules to justify the request. They argue that Congress intended the Vaccine Act to alleviate the liability exposure of vaccine companies, but that it never envisioned that these companies would be wholly exempt from discovery in a Vaccine Court proceeding. With all due respect, the statutory framework and legislative history that will be discussed below makes clear that Congress was concerned with precisely these types of expensive litigation burdens, not just final judgments. In fact, there is no precedent for guiding the Special Master in addressing many of the substantive and

logistical problems raised by Petitioners' request because the Vaccine Act was designed to exclude the vaccine companies from proceedings in this Court.

Keeping this important legislative backdrop in mind, Merck and the amici have each demonstrated in their prior briefs that the statutory and judicial standards that stand as a precondition to any discovery in this Court raise a high bar when applied to parties to a Vaccine Court proceeding. That burden is necessarily and additionally elevated when the object of discovery is a non-party—especially a non-party like Merck and the amici whom the Vaccine Act was enacted to protect. The only reasonable interpretation of Congress' intent is that resort may be made to discovery—at least as to third-parties covered by the Vaccine Act—only when there is a "gap" in the proof necessary to establish entitlement to compensation and the particular information that is lacking cannot be acquired another way.

Petitioners deftly try to convert the factual "gap" explained by Merck and the amici into a wholly unsubstantiated "scientific gap" theory. According to Petitioners, they are entitled to have access to the records of vaccine manufacturers whenever the available science is insufficient to support their burden of showing causation. That interpretation flies in the face of the Vaccine Act's structure and purpose. As SB explained in its amicus brief at 3-4, the Act envisions that Petitioners will assemble the available proof in a compensation proceeding, and the Special Master will determine whether it proves causation.

Petitioners maintain that the available studies themselves have identified "scientific gaps" that Petitioners assert can only be filled in with documents that may or may not exist in the vaccine companies' files. Specifically, they point to the October 2001 Report of the Institute of Medicine ("IOM Report") and remarks found on the website for FDA's Center for Biologics Evaluation and Research ("CBER"). Yet they fail to address the numerous recent studies that ***are*** publicly available—and with good reason. The wealth of available scientific data has closed

the gaps in science identified in the 2001 IOM Report, but Petitioners understandably find it lacking since the legitimate science tends to refute, rather than substantiate, their theory of causation. Petitioners' dissatisfaction with the scientific data that is publicly available provides no basis for subjecting the vaccine companies to the significant burden of responding to broad discovery requests in a proceeding that Congress deliberately exempted them from being part.

ANALYSIS AND AUTHORITIES

A. Plaintiffs Have Failed to Articulate a "Necessity" that Would Warrant Broad and Invasive Access to the Vaccine Companies' Files

Petitioners' argument as to why the documents they seek are "reasonable" and "necessary" starts with the premise that "the Special Master and petitioners [do not] have all the relevant evidence needed to conclude the causation analysis." Petitioners' Response at 3. From there, they proceed to dismiss the documents provided by the HHS Secretary thus far as providing only "a paucity of causation evidence." *Id.* Thus, Petitioners urge, "the Special Master needs to look elsewhere for the information." *Id.* Since "one may sensibly assume that Merck . . . is a reasonable place for the Special Master to turn," Petitioners conclude they have established the showings of necessity and reasonableness required to entitle them to discovery. *Id.*

The foundational assumption of Petitioners' analysis—that they are presumptively entitled to discover "all relevant evidence needed to conclude the causation analysis"—is where they first go astray of the Vaccine Act. The standard they articulate speaks to traditional discovery—not the presumptively limited role of discovery placed upon Vaccine Court proceedings. *Compare see* FED. R. CIV. P. 26(b)(1) ("Parties may obtain discovery regarding any matter, not privileged, that is relevant to the claim or defense of any party . . . ."), *with* 42 U.S.C. § 300aa-12(d)(2)(E) (mandating that the Vaccine Court rules "provide for limitations on

discovery and allow the special masters to replace the usual rules of discovery in civil actions in the United States Court of Federal Claims"). The fact that Merck may have "relevant" information does not make it reasonable or necessary to require Merck to seek out and produce wide-ranging materials from its extensive files.

Although Petitioners suggest that they "need only describe the information gaps identified in the respondent's own document production to provide a sufficient showing of necessity for the authorization to issue . . . the requested subpoena," Petitioners' Response at 3, notably, they point only to the IOM Report dated more than two years ago and remarks taken from the CBER website to identify those "information gaps." *Id.* at 4. Petitioners suggest that those "gaps" might possibly be filled in by information in the control of the vaccine companies. In fact, in the last two years, there have been numerous articles and studies on the very subjects that Petitioners itemize from the 2001 IOM Report. In the Research and Articles Summary and Appendix that is separately bound and being submitted contemporaneously, SB has summarized and attached abstracts and articles reporting on a number of recent studies and scientific data gathered in connection with research into the existence of any causative link between thimerosal and autism-related disorders. There have also been statements issued by various national and international agencies charged with vaccine safety after research has been presented to those agencies on those same subjects. As the lengthy appendix attests, there is a wide body of scientific knowledge on the subject, and Petitioners should be required to identify the specific gaps in that information—not resort to a two-year old IOM Report—before they can begin to surmount the compelling presumptions against third-party discovery from vaccine companies.

B. Merck's "Familiarity" With its Vaccine Product Goes to "Relevance" Not "Necessity"

Petitioners argue that "Merck's familiarity with the Recombivax product that it designed, tested, manufactured, and distributed for over a decade is an additional reason for allowing the requested discovery." Petitioners' Response at 5. If Petitioners' proposed standard were adopted, it would be hard to imagine a case involving a vaccine-related injury where that same showing could not be made. Again, Petitioners resort to relevance discovery standards, which are inapplicable in this Court.

Nonetheless, Petitioners attempt to draw support from a prior decision of this Court, *Wittner v. Sec'y Dept. of Health and Human Servs.*, 43 Fed. Cl. 199 (1999), in which a Special Master permitted the testimony of a consulting expert witness over the objection of the petitioner in that case. The consulting expert had been the treating physician for the injured child. The fact that non-party evidence was allowed in that case provides no basis for the discovery sought here. There is no claim that any vaccine company has particularized knowledge of the specific injuries or treatment of any petitioner in this case—only that the vaccine companies "might" have some materials in their possession that Petitioners hope might compromise the profusion of available scientific data that points away from any causal connection. Notably, Petitioners themselves do not claim to be aware that this information actually exists; they speculate only that if they could review the vast files of the vaccine companies, they might find something useful. But without even a hint as to what that information might be, their request to plow through hundreds of thousands of documents to see if it even exists is decidedly unreasonable.

C. The Balancing of the Respective Interests and Burdens Clearly Favors the Vaccine Companies

Petitioners appear to believe that it is "necessary" to go directly to the files of the vaccine companies since the production of PLAs by the government has taken so long. They argue that

the delay in production means delay in compensating so many injured children. Petitioners' Response at 8-9. But the solution they offer—shifting the burden of large-scale discovery to the vaccine companies—would not provide any real remedy and certainly is not grounds for putting the vaccine companies to this monumental task under the circumstances. As explained in the prior briefing, Petitioners are no more likely to get these documents more quickly from the vaccine companies than from the government, which has already been far down the road in compiling the PLA documents and negotiating trade secret redactions with the vaccine companies. Although Merck suggested potential ways to speed up the process—such as allowing the government to produce the PLA documents as currently redacted so that Petitioners can determine if the trade secrets are really worth fighting about—Petitioners do not even respond. If they truly want the majority of PLA documents sooner, it is curious that they will not consider more productive and less intrusive means to obtain them.

Finally, in their balancing-of-the-equities analysis, Petitioners suggest that the Vaccine Act was designed to prevent vaccine companies from liability exposure, not litigation burdens. Petitioners Response at 1, 9-10. In this assumption, they are simply wrong. Congress was clear that the litigation costs were an equally compelling reason for the Compensation Program: "Lawsuits and settlement negotiations can take months and even years to complete. ***Transaction costs—including attorneys' fees and court payments—are high.***" H.R. Rep. 99-908, at 6-7, *reprinted in* 1986 U.S. CODE, CONG. & ADMINISTRATIVE NEWS ("U.S.C.C.A.N.") 6344, 6347 (emphasis added). This sought-after discovery will force the vaccine companies to incur precisely the types of litigation transactional costs that Congress intended be avoided.

CONCLUSION

Petitioners have failed to show that the discovery they request is reasonable or necessary under the circumstances. Their request for a subpoena should be denied.

30615566.2

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on December 29, 2003, I served the foregoing Reply by Amicus SmithKline Beecham Corporation d/b/a GlaxoSmithKline to Petitioners' Response to Merck and Amicus Curiae re: Non-Party Discovery on the following individuals via facsimile and email transmission:

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December 29, 2003

VIA HAND DELIVERY

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717 Madison Place, NW
Washington, DC 20005-1011

Re: *In Re: Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder, or in a Similar Neurodevelopmental Disorder v. Secretary of Health and Human Services*; In the United States Court of Federal Claims, Office of the Special Master, Autism Master File

Dear Clerk:

Enclosed please find the original and three copies each of the following:

- Reply By Amicus SmithKline Beecham Corporation d/b/a GlaxoSmithKline to Petitioners' Response to Merck and Amicus Curiae re: Non-Party Discovery; and
- Research and Articles Summary and Appendix.

Please file the enclosed in your usual manner, returning file-stamped copies of each to me via the courier provided.

Thank you for your attention to this matter. If you have any questions, please do not hesitate to contact me at (512) 536-5216.

Very truly yours,

Marcy Hogan Greer

MHG/lak
Enclosures

30616937.1

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OFFICE OF SPECIAL MASTERS

IN RE: CLAIMS FOR VACCINE INJURIES RESULTING IN AUTISM SPECTRUM DISORDER, OR A SIMILAR NEURODEVELOPMENTAL DISORDER,	*	Autism Master File
Various Petitioner(s)	*	
v.	*	**REPLY BY AMICUS SMITHKLINE BEECHAM CORPORATION D/B/A GLAXOSMITHKLINE TO PETITIONERS' RESPONSE TO MERCK AND AMICUS CURIAE RE: NON-PARTY DISCOVERY**
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* *	*	

RESEARCH AND ARTICLES SUMMARY AND APPENDIX

Respectfully submitted,

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INDEX AND BIBLIOGRAPHY

A. Research and Articles Summary

1. Burbacher, TM, et al. Mercury levels in blood and brain of infant monkeys exposed to thimerosal [Abstract]

2. Clarkson TW, et al. Human exposure to mercury: the three modern dilemmas. *J. Trace Elements Exper. Med.* 2003;16:321-43.

3. Clarkson TW, et al. The toxicology of mercury --- current exposure and clinical manifestations. *N. Eng. J. Med.* 2003;349:1731-37.

4. Geier MR and Geier DA. Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. *J. Am. Phys. and Surgs.* 2003; 8(1):6-11.

5. Holmes AS, et al. Reduced levels of mercury in first baby haircuts of autistic children. *Int'l J. of Toxic.* 2003;22:277-85.

6. Hviid A, et al. Association between thimerosal-containing vaccine and autism. *JAMA* 2003;290(13):1763-66.

7. Madsen KM, et al. Thimerosal and the occurrence of autism: Negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112(3);604-06.

8. Magos L. Neurotoxic character of thimerosal and the allometric extrapolation of adult clearance half-time to infants. *J. Applied Toxicology* 2003;23:263-69.

9. Nelson KB and Bauman ML. Thimerosal and autism? *Pediatics* 2003; 111(3):674-79.

10. Pichichero ME, et al. Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study. *Lancet* 2002;360:1737-42.

11. Statement from the Committee on Safety of Medicines, Further Data Support Safety of Thiomersal in Vaccines. UK Medicines Control Agency, February 12, 2003.

12. Stehr-Green P, et al. Autism and thimerosal-containing vaccines: Lack of consistent evidence for an association. *Am. J. Prev. Med.* 2003;25(2):101-06.

13. Verstraeten T, et al. Safety of thimerosal-containing vaccines: A two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112(5):1039-48.

14. WHO Global Advisory Committee on Vaccine Safety. Statement on thiomersal. August 2003.

CERTIFICATE OF SERVICE

I hereby certify that on December 29, 2003, I served the foregoing Research and Articles Summary and Appendix on the following individuals via facsimile and email transmission:

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A

RESEARCH AND ARTICLES SUMMARY

As mentioned in SB's reply brief, Petitioners' eight alleged "gaps," listed in bullet point fashion on page 4 of their Response, are considered, *seriatim* and in the context of available scientific information, below. The referenced abstracts or articles are included in the attached bibliography for the Special Master's convenience:

1. "'The data regarding toxicity of low doses of thimerosal and ethyl-mercury are very limited, and only delayed-type hypersensitivity reactions have been demonstrated.'"[1]

Since the IOM Report, the following studies have appeared in peer-reviewed publications:

- Pichichero ME, et al. Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study. *Lancet* 2002;360:1737-42.

Dr. Pichichero and colleagues measured mercury levels in blood, urine and stool samples from 40 infants who received thimerosal-containing vaccines and compared them to 21 control infants receiving thimerosal-free vaccines. In addition to demonstrating that infants rapidly excrete a substantial portion of thimerosal-derived mercury in their feces, the researchers found that the "amounts of mercury in the blood of infants receiving vaccines formulated with thimerosal are well below concentrations potentially associated with toxic effects."

- Magos L. Neurotoxic character of thimerosal and the allometric extrapolation of adult clearance half-time to infants. *J. Applied Toxicology* 2003;23:263-69.

This article noted a significant difference between ethylmercury and methylmercury in terms of their ability to cross the blood-brain barrier. The author noted that it appeared from large dose poisoning data that "ethylmercury is less toxic than methylmercury" based on the amount necessary to produce the toxic effect.

- Clarkson TW, et al. The toxicology of mercury --- current exposure and clinical manifestations. *N. Eng. J. Med.* 2003;349:1731-37.

In this article, the authors compared the clinical toxicologic features of mercury vapor, methylmercury, and ethylmercury found in fish, dental amalgams, and vaccines, respectively. Concerning the vaccine issue, the authors noted the differences between the effects of methylmercury and ethylmercury and concluded:

> [I]n the two-month periods between vaccinations (at birth and at two, four and six months), all of the mercury should have been excreted, so that there is no accumulation.

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[1] Petitioners' Response at 4 (quoting *Immunization Safety Review: Thimerosal Containing Vaccines and Neurodevelopmental Disorders*, Institute of Medicine, October 2001 ["IOM Report"] at 3, 27).

This finding of no accumulation of mercury in blood with successive administration of thimerosal-containing vaccines has been demonstrated in the Burbacher, et al. study of non-human primate infants, discussed below.

- Clarkson TW, et al. Human exposure to mercury: the three modern dilemmas. *J. Trace Elements Exper. Med.* 2003;16:321-43.

Here, the same authors discussed the same issues in considerably more detail. As respects thimerosal in vaccines, they conclude: "Ethyl mercury and therefore thimerosal would appear to be less toxic in humans than methyl mercury compounds."

2. "There is a need for 'far more evidence of the risks and benefits associated with thimerosal-bearing vaccines.'"[2]

This quote is ostensibly lifted from the IOM's discussion of the "Public Health Response" (IOM Report, p. 7), which was the appropriate place for the IOM to focus on balancing risks and benefits. However, Petitioners have misquoted the Institute. The precise and complete statement of the IOM is: "There is a need for[3] more evidence on the risks and benefits associated with thimerosal-containing vaccines, biological, and pharmaceutical products in use in the United States and elsewhere." This "gap" has also been filled since October 2001.

- WHO Global Advisory Committee on Vaccine Safety. Statement on thiomersal. August 2003.

The IOM's expressed concern about risks/benefits "elsewhere" (which Petitioners omitted) is demonstrated in this position paper of the GACVS, which was established in 1999 by the World Health Organization to respond "promptly, efficiently and with scientific rigour to vaccine safety issues of potential global importance." After considering data presented by reknowned thimerosal researchers, including Dr. Pichichero, as well as the article by Geier and Geier discussed below, the GACVS determined that "there is no reason on the grounds of safety to change current immunization practices with thiomersal-containing vaccines, since ***the benefit outweighs any unproven risks***." (emphasis supplied.)

- Statement from the Committee on Safety of Medicines, Further Data Support Safety of Thiomersal in Vaccines. UK Medicines Control Agency, February 12, 2003.

This Committee considered two UK epidemiological studies and the Pichichero study (discussed above). The CSM Chairman stated: "The balance of benefits and risks of thiomersal-containing vaccines therefore remains ***overwhelmingly*** positive." (emphasis supplied.)

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[2] Petitioners' Response at 4 (purportedly quoting IOM Report at 7).

[3] Note the absence of the adjective "far" in the IOM Report.

3. **"The IOM 'is unaware of risk assessments of thimerosal in pharmaceutical products' and recommends risk-based research."**[4]

The risk/benefit studies referred to in 2 above are also applicable here.

4. **"The report discusses at length the lack of data regarding the toxicity or safety of ethyl mercury, the primary constituent of thimerosal."**[5]

By reiterating the same "gap" with a different characterization, Petitioners appear to be itemizing a greater number of gaps than ever existed. This "gap" is essentially the same as the one discussed in #1. The studies referenced above (Pichichero, et al., Magos, and the two Clarkson, et al. papers) speak directly to this point.

5. **"The report further details the lack of information about low doses of thimerosal, particularly noting the absence of toxicity data for the doses of thimerosal found in the pediatric vaccine schedule."**[6]

The 2002 Pichichero study, discussed above at #1, provides precisely the kind of data the IOM said was lacking. It is a study of exposure of infants who received the low dose of thimerosal that is in fact found in the vaccines.

- Burbacher, TM, et al. Mercury levels in blood and brain of infant monkeys exposed to thimerosal [Abstract]

This recent study in non-human infant primates compared the distribution of mercury in newborn monkeys following intramuscular administration of thimerosal-containing vaccines as compared to oral methylmercury ingestion. Dr. Burbacher and colleagues concluded that "EPA guidelines for methylmercury exposure may not provide an accurate assessment of the public health risk to children receiving thimerosal-containing vaccines."

6. **"The IOM explicitly recognizes the gaps in science by recommending a number of biomedical,[7] clinical, epidemiological, and basic science research areas in order to develop the evidence."**[8]

Summarized in Box ES-1 (IOM Report, pp. 14-15) are the IOM's recommendations of "a diverse public health and biomedical research profile" consisting of Epidemiological Research, Clinical Research and Basic Science Research. What has transpired since the IOM Report is outlined below.

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[4] Petitioners' Response at 4 (quoting IOM Report at 9).

[5] *Id.*

[6] *Id.*

[7] Petitioners have confused the classifications intended by the IOM by suggesting that "biomedical" research is a separate category.

[8] Petitioners' Response at 4.

Epidemiology

Epidemiological studies have been completed with respect to thimerosal:

- Stehr-Green P, et al. Autism and thimerosal-containing vaccines: Lack of consistent evidence for an association. *Am. J. Prev. Med.* 2003;25(2):101-06.

Dr. Stehr-Green and colleagues performed an ecological study analyzing the reported increases in autism in California, Sweden and Denmark over comparable periods of time. Sweden and Denmark were chosen because in those countries, childhood vaccines have been thimerosal-free since 1993. Both Sweden and Denmark reported increases in the number of diagnosed cases that continued, and even accelerated, after the 1993 removal of thimerosal from childhood vaccines. Recognizing that there are limitations on ecological analyses, the authors concluded that the evidence to date and their data "are not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines are responsible for the apparent increases in the rates of autism in young children being observed worldwide."

- Madsen KM, et al. Thimerosal and the occurrence of autism: Negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112(3);604-06.

These investigators performed the same type of analysis as did the Stehr-Green study but focused solely on Denmark. They note that "the thimerosal-containing vaccine was gradually phased out meaning that the incidence rates should decline gradually if thimerosal has any impact on the development of autism. However, an increase (rather than a decrease) in the incidence rates of autism was observed."

- Hviid A, et al. Association between thimerosal-containing vaccine and autism. *JAMA* 2003;290(13):1763-66.

This study also focused on Denmark but took a different approach. It is a cohort study comparing the numbers of children diagnosed with autism who were vaccinated with thimerosal-containing vaccines to those who were vaccinated without thimerosal. They found that the risk for autism did not differ significantly between the two groups. They also found no evidence of a dose-response relationship (where those who got higher doses of thimerosal were at increased risk for autism). The authors concluded that "our results are not compatible with the hypothesis of a causal association between thimerosal and autistic-spectrum disorders."

- Verstraeten T, et al. Safety of thimerosal-containing vaccines: A two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112(5):1039-48.

This study was a retrospective cohort study of neurodevelopmental disorders in three HMOs in which assessments were made at different times during development based on the amount of thimerosal received. The study concluded: "No consistent significant associations between [thimerosal-containing vaccines] and neurodevelopmental outcomes were found" among the HMOs.

- Geier MR and Geier DA. Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. *J. Am. Phys. and Surgs.* 2003; 8(1):6-11.

The lead author of this article is well known to this Court. *See Daly v. Secretary of HHS*, No. 90-590V, 1991 WL 154573, n.11 (Chief Spec. Mstr. Golkiewicz): "[T]he court admonishes Dr. Geier to reconsider his role, from a moral standpoint, as a witness under this Program."

The authors claim that their analyses provide "strong epidemiological evidence for a link between mercury exposure from thimerosal-containing vaccines and neurodevelopmental disorders." However, these analyses have been severely criticized by the American Academy of Pediatrics ("Study fails to show a connection between thimerosal and autism"), the National Immunization Program ("The researchers inadequately described the methods they used, making it impossible to determine exactly what was done and how the results should be interpreted. . . . There are a number of weaknesses in this analysis, including an apparent misunderstanding among the authors regarding VAERS reporting requirements.") and GACVS ("[T]he article does not provide a sufficient scientific basis for changing the WHO policy in respect of thiomersal-containing vaccines.").

Among these concerns was the Geiers' use of the Vaccine Adverse Event Reporting System ("VAERS").[9] As the CDC explained in a recent report:

> Passive surveillance systems (e.g., VAERS) are subject to multiple limitations, including underreporting, reporting of temporal associations or unconfirmed diagnoses, and lack of denominator data and unbiased comparison groups. Because of these limitations, determining causal associations between vaccines and adverse events from VAERS reports is usually not possible.

CDC. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System [VAERS] --- United States, 1991-20001. *MMWR* 2003;52[SS-1]:1-24. The IOM has also expressed concern that "VAERS and other case reports submitted to the committee are useful for hypothesis generation, but they are generally inadequate to establish causality." IOM Report, p. 59.[10]

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[9] VAERS is a passive surveillance system meaning that reports are voluntarily submitted by those who witness the adverse events, including practitioners, parents, hospitals, even attorneys.

[10] Other Geier articles suffer from the same deficiencies. *See, e.g.*, Geier MR and Geier DA. Neurodevelopmental disorders after thimerosal-containing vaccines: A brief communication. *Exp. Biol. Med.* 2003;228(6): 660-64; Geier DA and Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Pediatr. Rehabil.* 2003;6(2):97-102.

Clinical Research

For clinical research, the IOM recommended three types of studies: (a) how children metabolize and excrete heavy metals, particularly mercury; (b) modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury from other exposures; and (c) "careful, rigorous and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism." IOM Report, p. 15. Several studies fit these categories:

- Pichichero, et al. *See* #1 above.

This previously described study specifically investigated the levels of mercury in the blood of infants administered thimerosal-containing vaccines and its subsequent excretion in feces.

- Holmes AS, et al. Reduced levels of mercury in first baby haircuts of autistic children. *Int'l J. of Toxic.* 2003;22:277-85.

These investigators compared the baby hair of 94 children eventually diagnosed with Autism Spectrum Disorder (ASD) to the baby hair of 45 controls. Lab testing determined the mercury content in the hair of the ASD children to be low compared to that of controls. The authors speculate that if mercury is not in the hair, it is still in the body and they "***presume*** that a portion of the tissue mercury retention is sequestered in the central nervous system." (emphasis added).

Basic Science Research

Here, the IOM focused on two specific categories: (a) research to identify an alternative to thimerosal "for countries that decide they need to switch"[11] and (b) research in animal models on neurodevelopmental effects of ethylmercury. IOM Report, p. 12. As respects animal models, studies are underway which have not yet resulted in published results. Abstracts of those studies have been presented at two International Meetings for Autism Research (IMFAR) in November 2001 and November 2002. Another animal model study by Burbacher, et al. (discussed above) has been abstracted and presented recently to the Advisory Committee on Immunization Practices. Copies of the abstracts of animal studies pertaining to thimerosal are included in this appendix.

7. "'Additional studies to fill in gaps in our knowledge, such as whether the regressive subtype of autism is causally related to thimerosal in vaccines, is warranted.'"[12]

The website for the Center for Biologics Evaluation and Research (CBER) states that the "U.S. Public Health Service agencies have collaborated with various investigators to initiate further studies to better understand any possible health effects from exposure to thimerosal in

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[11] Petitioners cannot be interested in research concerning preservatives other than thimerosal since they need to prove a causal connection to thimerosal-containing vaccines.

[12] Petitioners' Response at 4 (quoting www.fda.cber.gov, "Frequently Asked Questions").

vaccines." www.fed.gov/cber. Since the government is the Respondent here, it should be the source of the information sought by the Petitioners.

- Nelson KB and Bauman ML. Thimerosal and autism? *Pediatics* 2003; 111(3):674-79.

This commentary relates to the claim that autism is a form of mercury poisoning based on a comparison of symptoms, as hypothesized by Bernard S, et al. Autism: a novel form of mercury poisoning. *Med. Hypothesis* 2001;56;462-71. The authors, a neuroepidemiologist at the NIH and a neurologist at Harvard Medical School, demonstrate that the Bernard, et al. symptom comparison is simplistic and flawed. Consistent with the Clarkson studies (*see* #1), they state: "At equivalent doses, higher levels of mercury have been found in the blood and less in brain following administration of ethylmercury than methylmercury."

Drs. Nelson and Bauman also note that the pathological differences of brains exposed to methylmercury poisonings have different appearances than those of autistic brains. The most dramatic difference is that brains involved in methylmercury poisonings are smaller than normal, while autistic brains are larger.

The final conclusion expressed by Drs. Nelson and Bauman is: "On the basis of current evidence, we consider it improbable that thimerosal and autism are linked."

Drs. Nelson and Bauman also make the point that there is no environmental conclusion to be drawn from the fact of regression, pointing out that even single gene disorders may have a period of apparently normal development. The dramatic example they cite is Huntington's chorea, where 45 years may pass before the onset of clinically recognizable signs. They state that with autism "the onset of signs in the second year of life does not prove (or disprove) a role for environmental factors in etiology."

8. "'Whether there is, or is not, any synergistic biological interaction between aluminum and mercury [in vaccine products] is unknown.'"[13]

The two sentences immediately preceding the one quoted by the Petitioners from the CBER website puts the aluminum issue in context:

> Over a period of 6 months, taking an average weight of 5 kilograms for a child, this [the ATSDR's minimal risk level] would translate into an allowed accumulation of 10.8 milligrams of aluminum. This number is in excess of the 1.5-3.5 milligrams of aluminum that a child would receive from vaccines.

www.fda.gov/cber/vaccine/thimfaq.htm. That being said, however, we have found no published research examining the potential for synergistic interactions between aluminum and mercury.

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[13] *Id.*

(Exhibits 1 through 14, attached to the Reply brief of Smith Kline, have been filed into the Master Autism File, but are not being placed on the website for the Omnibus Autism Proceeding due to the provisions of 42 U.S.C. § 300aa-12(d)(4)(A).)