DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

JAN 18 2018

Mr. Del Bigtree
Informed Consent Action Network
10200 US HWY 290 W, Suite 301
Austin, Texas 78736

Dear Mr. Bigtree:

Acting Secretary Hargan has asked me to thank you for your letter expressing interest in vaccine safety and in and the federal policies guiding the licensing, recommendation, and safety monitoring of immunizations, and to respond to you directly.

The Department of Health and Human Services has a far-reaching mission to enhance and protect the health of all Americans. Vaccines are held to the highest standard of safety to both protect people from adverse reactions and enhance their health by preventing a number of serious diseases. I am proud to report that data show the United States currently has the safest supply in history.

I have provided responses to your specific questions in the enclosure to this letter. Thank you for the opportunity to address your concerns.

Sincerely yours,

Melinda Wharton

Melinda Wharton, MD, MPH
Acting Director, National Vaccine Program Office

Enclosure

HHS Responses to Questions and Comments from Mr. Bigtree

I would like to address a comment made in section II of your letter about pre-licensure safety review of pediatric vaccines. Contrary to statements made on page two of your letter, many pediatric vaccines have been investigated in clinical trials that included a placebo. In addition, there appears to be a misunderstanding regarding the term "solicited" adverse events. Typically, in vaccine trials, the incidence of certain specific clinical findings that might be expected after vaccination is monitored for a short period of time after vaccination. Because these events are pre-specified, they are considered to be "solicited" events. In addition, other unexpected or severe adverse events, which may occur over a longer period of time following vaccination, are also analyzed and evaluated by FDA, but because these events are not predicted prior to initiation of the study, these are not called "solicited" adverse events. Please be assured that vaccine safety is carefully examined regardless of whether there is a placebo included in the clinical trials. Once vaccines are approved, the safety is also carefully monitored, in some cases by manufacturer-conducted post-marketing studies by Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), or the Post-licensure Rapid Immunization Safety Monitoring System (PRISM), as well as other mechanisms.

(1) Please explain how HHS justifies licensing any pediatric vaccine without first conducting a long-term clinical trial in which the rate of adverse reactions is compared between the subject group and a control group receiving an inert placebo?

Inert placebo controls are not required to understand the safety profile of a new vaccine, and are thus not required. In some cases, inclusion of placebo control groups is considered unethical. Even in the absence of a placebo, control groups can be useful in evaluating whether the incidence of a specific observed adverse event exceeds that which would be expected without administration of the new vaccine. Serious adverse events are always carefully evaluated by FDA to determine potential association with vaccination regardless of their rate of incidence in the control group. In cases where an active control is used, the adverse event profile of that control group is usually known and the findings of the study are reviewed in the context of that knowledge.

(2) Please list and provide the safety data relied upon when recommending babies receive the Hepatitis B vaccine on the first day of life?

Data relied upon in licensing infant use of hepatitis B vaccines is summarized in the respective package inserts. Furthermore, pediatric data from other countries and in the literature, support the safety of these vaccines in infants. The recommendation for all children to receive these vaccines was made by the Advisory Committee for

Immunization Practices. Their reasoning is summarized in a *Morbidity and Mortality Weekly Report* at https://www.cdc.gov/mmwr/preview/mmwrhtml/00033405.htm. Follow-up studies support the safety of infant vaccination with hepatitis B vaccines.

(3) Please explain why HHS failed to cooperate with Harvard to automate VAERS reporting? And detail any steps that HHS has taken since toward automating VAERS reporting?

On June 30, 2017, the Centers for Disease Control and Prevention (CDC) and FDA implemented a revised reporting form and a new process for submitting reports to the VAERS for non-manufacturer reports. Persons reporting adverse events are now able to use the VAERS 2.0 online reporting tool to submit reports directly online; alternatively, they may download and complete the writable and savable VAERS 2.0 form and submit it using an electronic document upload feature. Vaccine manufacturers submit VAERS reports electronically through the FDA Electronic Submissions Gateway (ESG). With VAERS 2.0 and the FDA ESG, multiple electronic options exist for VAERS reporting.

In addition, CDC is developing the next generation of spontaneous reporting mechanisms for the VAERS. Following its initial work with Harvard, CDC completed a successful proof of concept study with Harvard and other partners that takes advantage of electronic health records (EHR) and computer algorithms to facilitate direct reporting from EHR systems. You can read about that study at https://academic.oup.com/cid/article/61/6/864/451758. CDC continues to explore options to further develop this capability.

(4) Please explain any specific steps taken by HHS to improve adverse reaction reporting to VAERS?

Please see my response to question #3.

(5) For each of the 38 vaccine-injury pairs reviewed in the 1994 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please refer to the latest review of the "Safety of Vaccines Used for Routine Immunization in the United States" published in 2014 at https://www.ahrq.gov/research/findings/evidence-based-reports/vaccinestp.html. This report reviewed and accepted the findings of the 2011 Institute of Medicine report and provides an independent, systematic review of the literature published after that report on the safety of vaccines recommended for routine immunization of children, adolescents,

and adults in the United States. The report, highlighted in the July 2014 issue of *Pediatrics*, provides the most comprehensive review to date of published studies on the safety of routine vaccines recommended for children in the United States. The report concludes that the risk of rare adverse events must be weighed against the protective benefits that vaccines provide. Furthermore, the Centers for Disease Control and Prevention (CDC) has been working to address several of the vaccine-injury pairs that have been identified in the reports mentioned above. A list of CDC vaccine safety publications can be found at: https://www.cdc.gov/vaccinesafety/research/publications/index.html.

(6) For each of the 135 vaccine-injury pairs reviewed in the 2011 IOM Report which the IOM found lacked studies to determine causation, please identify the studies undertaken by the HHS to determine whether each injury is caused by vaccination?

Please see response to question #5.

(7) Please explain what HHS has done to assure that health care providers record the manufacturer and lot number for each vaccine they administer?

Health care providers who administer vaccines covered by the National Vaccine Injury Compensation Program (VICP) are required under the National Childhood Vaccine Injury Act of 1986 (Vaccine Act), as amended, to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine. This provision of the Vaccine Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine). In addition, the provider is required to record the edition date of the Vaccine Information Statement (VIS) distributed and the date those materials were provided.

The Advisory Committee on Immunization Practices (ACIP) also issued "General Best Practice Guidelines for Immunization" at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/records.html. This report provides information for clinicians and other health care providers about concerns that commonly arise when vaccinating persons of various ages, and includes a chapter on vaccination records that reinforces the Vaccine Act's requirement to record in the recipient's medical record (or a permanent office log or file) the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine.

(8) Please advise when HHS intends to begin conducting research to identify which children are susceptible to serious vaccine injury? If HHS believes it has commenced this research, please detail its activities regarding same?

HHS is currently supporting several initiatives that focus on advancing research on the fields of precision vaccinology (vaccine formulations tailored on the individual immune reactivity status) and adversomics (the study of vaccine adverse reactions using immunogenomics and systems biology approaches). Two examples are listed below:

- https://www.immuneprofiling.org/hipc/page/showPage?pg=about
- https://www.hhs.gov/nvpo/national-vaccine-plan/funding-opportunity-vaccine-safety-research/index.html

(9) Please confirm that HHS shall forthwith remove the claim that "Vaccines Do Not Cause Autism" from the CDC website, or alternatively, please identify the specific studies on which HHS bases its blanket claim that no vaccines cause autism?

Vaccines are held to strict standards of safety. Many studies have looked at whether there is a relationship between vaccines and autism spectrum disorder (ASD). These studies continue to show that vaccines do **not** cause ASD. For more information, please refer to the literature below:

- https://www.cdc.gov/vaccinesafety/pdf/cdcstudiesonvaccinesandautism.pdf
- http://nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx
- http://www.jpeds.com/article/S0022-3476(13)00144-3/pdf?ext=.pdf
  http://nationalacademies.org/HMD/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

While there is still a lot to learn about ASD, research from public and private organizations indicate that environmental and genetic factors may increase the risk of autism, not vaccines or vaccine ingredients. HHS continues to research this issue to search for answers to better understand the risk factors and causes of this disease. Recent efforts to coordinate autism research are reflected in the "Strategic Plan for Autism Spectrum Disorder Research" by the Interagency Autism Coordinating Committee at https://iacc.hhs.gov/publications/strategic-plan/2017/.

(10) Please advise whether HHS intends to forthwith conduct adequately powered and controlled prospective as well as retrospective studies comparing total health outcomes of fully/partially vaccinated with completely unvaccinated children?

HHS tasked the Institute of Medicine (IOM) to identify research approaches, methodologies, and study designs that could address questions about the safety of the current schedule. This report is the most comprehensive examination of the immunization schedule to date and can be found at http://nationalacademies.org/HMD/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx. The IOM committee uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule. The committee also cited ethical concerns about conducting a new study to compare the health outcomes of vaccinated children with their fully unvaccinated counterparts, as this would intentionally leave unvaccinated people and the communities they live in subject to increased risk of death and illness.

Should signals arise that there may be need for investigation, however, the report offers a framework for conducting safety research using existing or new data collection systems. One of the systems that the IOM report considered best suited to conduct these types of studies is CDC's Vaccine Safety Datalink (VSD). In response to the IOM report, CDC commissioned a white paper on the feasibility of conducting studies of the safety of the vaccine schedule in VSD. This report states, "Additionally, CDC has started conducting some of the studies mentioned in the white paper." Additional information on the white paper can be found at: https://www.cdc.gov/vaccinesafety/pdf/whitepapersafety_web.pdf.

(11) Please advise if you will:

a. prohibit conflict waivers for members of HHS's vaccine committees (ACIP, VRBPAC, NVAC & ACCV)?

HHS employs a thorough process for soliciting and vetting candidates for advisory committees to minimize any potential for financial conflicts of interest and works to identify all potential financial conflicts related to the particular matter before a committee. In accordance with 18 U.S.C. § 208(b)(1) and (b)(3), a member of an HHS vaccine advisory committee may be granted a waiver to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met. See 18 U.S.C. § 208 for more information.

b. prohibit HHS vaccine committee members or HHS employees with duties involving vaccines from accepting any compensation from a vaccine maker for five years?

The current federal ethics laws and regulations do not provide HHS or any other federal agency the authority to restrict the future employment of a career federal employee or an advisory committee member after they leave federal service. However, there are some restrictions on communication by former employees back to their federal agency, such as

a lifetime ban on communicating or appearing before the government on behalf of their new employer or anyone else regarding specific policy matters in which they participated personally and substantially during their entire government service. See 18 U.S.C § 207(a)(1) for more information. There are a number of other exceptions that may apply as well including restrictions on representations to the government for matters under the former employee's official responsibility and restrictions that apply to senior-level government officials.

Federal advisory committee members and career federal employees are prohibited from participating personally and substantially in a particular government matter that will affect their financial interests, as well as the financial interests of their spouse or minor child, general partner, or groups or people covered by 18 U.S.C. § 208. Many federal employees, depending on their duties, must file financial disclosure reports to help identify and mitigate potential conflicts of interest with the employees' duties. See 5 CFR Part 2634. Additionally, special government employees serving on advisory committees must report certain financial interests before attending committee meetings. *See* 5 CFR § 2634.904(a)(2). A 208(b)(3) waiver may be granted to such committee members, based on a determination that the need for the service outweighs the potential for a conflict of interest.

c. require that vaccine safety advocates comprise half of HHS's vaccine committees?

The Vaccine Act defines memberships for the NVAC and ACCV. See 42 U.S.C. §§ 300aa-5 and 300aa-19. The VRBPAC charter states that "Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology; bacteriology, epidemiology or biostatistics, vaccine policy, vaccine safety science, federal immunization activities, vaccine development including translational and clinical evaluation programs, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry." You can learn more about the VRBAC charter at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129571.htm. The ACIP charter provides that "the committee shall consist of 15 members, including the Chair. Members and the Chair shall be selected by the Secretary, HHS, from authorities who are knowledgeable in the fields of immunization practices and public health, have expertise in the use of vaccines and other immunobiologic agents in clinical practice or preventive medicine, have expertise with clinical or laboratory vaccine research, or have expertise in assessment of vaccine efficacy and safety. The committee shall include a person or persons knowledgeable about consumer perspectives and/or social and community aspects of immunization programs." You can find out more about the ACIP by reading the charter at

https://www.cdc.gov/vaccines/acip/committee/charter.html. New members are selected based on the candidate's qualifications and their ability to contribute to the specific objectives or needs of the committee, with an overall goal of ensuring a diverse committee that reflects the charge.

d. allocate toward vaccine safety an amount at least equal to 50% of HHS's budget for promoting/purchasing vaccines?

The United States has a robust vaccine safety system that closely and constantly monitors the safety of vaccines. Several agencies within HHS dedicate a significant portion of their budgets and expertise to collaboratively ensure that vaccination efforts are as safe as possible. Due to the significant progress made in the last few years to monitor side effects and conduct relevant vaccine safety research, HHS does not foresee drastically changing current budget allocations in this area. However, this could change pending a vaccine safety signal. Likewise, advances in the development of new vaccines or ways of administering immunizations may require additional vaccine safety funding.

To address comments you made in your letter about vaccine monitoring, I want to clarify a few things. The Vaccine Adverse Event Reporting System (VAERS) is a national system to collect reports of adverse events that happen after vaccination. The adverse events reported to this system are not necessarily caused by vaccination and may or may not be a condition that occurred by chance alone, so they must be further investigated. For more information, please visit: https://vaers.hhs.gov/.

HHS places a priority on vaccine safety. To fulfill public health and regulatory functions, the Centers for Disease Control and Prevention (CDC) and FDA use the Vaccine Safety Datalink (VSD) and Post-licensure Rapid Immunization Safety Monitoring System (PRISM) to evaluate if adverse events are related to vaccination. You can find more details about VSD and PRISM at:
https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html and
http://onlinelibrary.wiley.com/doi/10.1002/pds.2323/abstract.

e. support the creation of a vaccine safety department independent of HHS?

HHS works in close partnership with other federal, state and local agencies, as well as private entities to monitor and communicate about the safety of U.S. vaccines. To adequately address safety-related issues, strengthen the system that monitors the safety of vaccines throughout production and use, and advance the safety profile of vaccines, the expertise of several groups within HHS is required. For example, FDA regulates vaccine clinical trials, licenses vaccines, and monitors vaccine safety after vaccine use and the Health Resources and Services Administration runs the National Vaccine Injury Compensation Program and the Countermeasures Injury Compensation Program. As HHS plays a significant and cross-cutting role in vaccine safety, the diverse federal

vaccine safety portfolio is coordinated at HHS to leverage collaboration among the many groups, inside and outside of HHS, involved in vaccine and immunization activities.

To address your point about conducting research to uncover long-term adverse events, HHS both conducts research in this area and funds outside research in this area. For example, after a safety signal in Europe indicated an increased risk of narcolepsy, a chronic neurological disorder caused by the brain's inability to normally regulate sleep-wake cycles, after vaccination with a monovalent 2009 H1N1 influenza vaccine, CDC began research to determine if there was a safety issue not only in the United States but globally as well. To respond to this signal, an international team of researchers conducted a dynamic retrospective cohort study to estimate incidence rates of narcolepsy diagnoses using a common protocol on electronic data in seven countries during 2003–2013. For the case control study, conducted according to a common protocol in six countries, cases were identified from sleep center records. Overall, the results of this study did not support an association between receipt of the 2009 H1N1 vaccine and narcolepsy. The successful completion of this study proves that the United States has the infrastructure to not only investigate vaccine safety signals at a local level, but to also collaborate with international partners when such signal is of global concern.

f. support the repeal of the 1986 Act to the extent it grants immunity to pharmaceutical companies for injuries caused by their vaccine products?
The National Vaccine Injury Compensation Program (VICP) does vital work to ensure an adequate supply of vaccines, stabilize vaccine costs, and establish and maintain an accessible and efficient forum for individuals found to be injured by certain vaccines. According to the VICP website, over 5000 petitions were compensated, supply shortages of vaccines have been reduced, and pricing of vaccines stabilized since the program was enacted. Likewise, this program provides an alternative to civil litigation that includes attorney fees and costs. Although the Vaccine Act provides liability protections to manufacturers of covered vaccines in many circumstances, these protections are not absolute. The Vaccine Act provides that there are instances when a manufacturer of a covered vaccine is not protected from liability by the Act, such as when an individual files a petition and is requesting damages of $1,000 or less. In such a case, a civil suit against an administrator may be permitted to be filed in state or Federal court without first filing a petition in the VICP.

Further, a repeal of the National Childhood Vaccine Injury Act of 1986 is unlikely. Congress recently passed the 21st Century Cures Act (Public Law 114-255), which made several amendments to the Vaccine Act. The amendments expand the VICP's coverage to include new vaccines that previously were not covered by the VICP (vaccines recommended by the CDC for routine administration in pregnant women) and make clear

that vaccine-injury claims may be filed both with respect to injuries alleged to have been sustained by women receiving covered vaccines during pregnancy and with respect to injuries alleged to have been sustained by live-born children who were in utero at the time those women were administered such vaccines.