



June 8, 2018

****VIA <https://www.regulations.gov>****

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Written Comment on 83 FR 15161, Docket No. FDA-2018-D-1201 - "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials; Draft Guidance; Availability."

Dear Dockets Management Staff,

The National Vaccine Information Center (NVIC) is the oldest and largest non-profit charity advocating for the prevention of vaccine injuries and deaths through public education and inclusion of informed consent protections in U.S. vaccine policies and laws and we respectfully submit this public comment to the Food and Drug Administration (FDA) on draft guidance for industry on "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials."

In reviewing the Draft Guidance for industry regarding scientific and ethical considerations for inclusion of pregnant women in clinical trials, although the word "vaccine" or "vaccinations" or "immunizations" does not appear in the Draft Guidance, the FDA categorizes vaccines as "biologics" or "biological products."¹ Vaccines appear to be addressed globally with one mention of biological products in line 20 of the introduction of the Draft Guidance. If this guidance document is to apply to the recruitment of pregnant women for inclusion in clinical trials of existing or new experimental vaccines, we strongly encourage integration of language specific to vaccines throughout the document, as there are inherent differences between clinical trial research to develop pharmaceutical drugs designed to treat illness and clinical trials of vaccines given to healthy pregnant women.

Young women who are pregnant or plan to become pregnant and give birth in the U.S. are at increased risk of dying during the birth process and within a year of giving birth and their newborns are at increased risk of dying within a year of birth. The U.S. has the worst infant and maternal mortality rates of all developed nations, even though 35-50 percent of women are receiving influenza and Tdap vaccines during pregnancy and more than 90 percent of newborns are receiving a hepatitis B vaccination at birth and, after birth, the majority of infants are being given at least 25 doses of eight CDC recommended vaccines in the first year of life.²

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Vaccines Already in Use During Pregnancy

In terms of ethical considerations regarding the current federal policy of recommending vaccination of all pregnant women with influenza and pertussis containing Tdap vaccines during every pregnancy, it should be noted that influenza vaccines and Tdap vaccines were not tested in or licensed for use in

pregnant women prior to the CDC's recommendation for their use by all pregnant women.^{8 9} Currently influenza and tetanus, diphtheria and pertussis vaccines are recommended for off label use during pregnancy by the Centers for Disease Control (CDC).¹⁰ The text of one vaccine manufacturer's prescribing information for use of Tdap vaccine in pregnant women highlights a critical lack of knowledge about the potential negative biological effects on the pregnant woman and her fetus, which appears to be common for vaccines administered to pregnant women:

“Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.” In addition, the following language is common in most vaccine manufacturer prescribing information inserts: “Adacel vaccine has not been evaluated for carcinogenic, mutagenic potential or impairment of fertility.”¹¹

Vaccines stimulate an inflammatory response in the body to produce artificial active immunity, yet inflammation is not desirable during pregnancy.^{12 13 14} The pregnancy vaccination policy has preceded the science and there continues to be a lack of credible biological mechanism evidence to demonstrate that administering influenza and pertussis containing Tdap vaccines to women during every pregnancy is safe.¹⁵ Scientifically, it remains unclear if the universal use policy is causing harm to pregnant women or adversely affecting normal fetal development and immune and brain function, as well as the integrity of the microbiome and epigenome, of the infant after birth.^{16 17 18 19 20 21 22}

Elimination of Vaccine Product Liability for Vaccines

The 21st Century Cures Act was passed by Congress and signed into law by President Barack Obama in December 2016.²³ That Act amended the National Childhood Vaccine Injury Act of 1986, which provided federal compensation for children injured by federally recommended and state mandated vaccines.²⁴ The 21st Century Cures Act indemnified vaccine manufacturers for product liability when there is evidence that a federally recommended vaccine (or vaccines) harmed a pregnant woman or an infant born alive was injured in the womb by a federally recommended vaccine(s) administered to the infant's mother.²⁵

There has been some speculation that this indemnification will encourage pharmaceutical companies to test experimental vaccines on pregnant women.²⁶ The fact that commercial pharmaceutical companies producing vaccine products will no longer be legally liable for harm caused to pregnant women or their infants during gestation if they are born alive is significant and increases the need for in-depth biological mechanism research and high pre-licensure standards for proof of safety of vaccines federally recommended for universal use in pregnant women. As pointed out in a 2017 review of ethical issues involved in vaccine research on pregnant women:²⁷

“As a fetus or infant cannot consent to participation in research, a critical issue is how much risk is acceptable to impose upon the fetus or the infant. For research with the potential of direct medical benefit to the woman or fetus, risk proportionate to the potential benefit is

acceptable. For research that does not involve the prospect of direct medical benefit, risk to the fetus must be no more than minimal. However, the definitions of minimal risk in the context of pregnancy are unclear.”

Primacy of informed consent in research

There are significant ethical issues that have been reviewed by public health officials related to enrolling pregnant women in vaccine studies, including study design and implementation, review board processes, information and risk disclosure and informed consent. ²⁸ A priority of any scientific experiment involving humans, especially pregnant women, should be obtaining informed consent from participants before research begins.

Initial statements in the background section set the tone for the draft guidance document. While federal informed consent ²⁹ requirements are mentioned elsewhere in the draft, the document should clearly acknowledge that pregnant women being recruited to participate in vaccine trial research have the legal and ethical right to fully exercise voluntary informed consent to being test subjects.^{30 31} Transparent full disclosure of all potential known and unknown risks to the pregnant woman and her unborn child should be mandatory in all research on pregnant women. Protecting this basic human right is of primary importance as clinical trial research on pregnant women is contemplated. NVIC recommends the following edit in blue be added to the document:

- Background, Line 62 – In the interests of promoting maternal/fetal health, **informed consent**, and informed prescribing conditions...

First Establishing Vaccine Safety and Effectiveness in Healthy Non-Pregnant Adult Women

Pregnant women, developing fetuses and newborns are among the vulnerable populations for which high standards for proof of necessity; safety and effectiveness of vaccines should first be established in non-vulnerable populations. ^{32 33} In reports published over the past 25 years, the Institute of Medicine (IOM), National Academy of Sciences, has repeatedly cited research gaps in vaccine safety science. ³⁴

Significantly, the IOM's 2012 report on *Adverse Effects of Vaccines: Evidence and Causality*, revealed that for 135 (85%) of serious adverse health outcomes associated with one or more of the federally recommended vaccines under examination, there was either an absence of or too little biological mechanism evidence and/or methodologically sound epidemiologic studies related to the vaccine and reported serious adverse health outcomes for the IOM committee to make a causation conclusion. ³⁵ The need for both credible biological mechanism and epidemiological evidence for vaccine safety to inform vaccine policy was emphasized:

“Even very large epidemiologic studies may not detect or rule out rare events. Subgroup analysis or more focused epidemiologic studies, informed by as yet incomplete knowledge of the biological mechanisms of vaccine-induced injury, may be required....The value of dialogue between both epidemiologic and mechanism approaches cannot be overstated. Epidemiologic studies can identify particular high risk groups, who can then be examined with more in depth testing to explore 21 of 40 predisposing factors. The findings of such studies can then inform more focused epidemiologic research as well as efforts to reduce risks. These conversations between different types of research can be difficult, but the results are worth it.”

The fact that there is individual susceptibility to vaccine adverse responses but doctors often cannot identify the genetic, biological and environmental factors, which raise vaccine risks for individuals due to lack of scientific knowledge about them, is also not acknowledged in this draft clinical trial guidance for industry.³⁶ This lack of basic understanding of the biological mechanisms and high risk factors for vaccine injury and death in individuals who are not pregnant hampers the ability to design ethical research into the biological effects of vaccination in pregnant women. The lack of published biological mechanism studies and well-designed prospective case controlled studies that assess immune and brain function and genetic integrity before and after adults or children are vaccinated is of great concern to those being directed to receive all federally recommended vaccines.³⁷ That justifiable concern is magnified when it comes to the potential adverse effects of vaccination on pregnant women and their unborn infants developing in the womb.

Most of the studies of vaccination during pregnancy are small,³⁸ retrospective,³⁹ ⁴⁰ comparing vaccinated women to unvaccinated women⁴¹ and performed by drug company or government health officials.⁴² Additionally, most studies of vaccination during pregnancy exclude high risk women. Among the exclusion criteria for one clinical study on the effects of pertussis vaccine in pregnant women was the following:⁴³

- Serious underlying medical condition (e.g., immunosuppressive disease or therapy, human immunodeficiency virus (HIV) infection, collagen vascular disease, diabetes mellitus, chronic hypertension, moderate to severe asthma, lung/heart disease, liver/kidney disease, chronic or recurrent infections).
- Significant mental illness (e.g. schizophrenia, psychosis, major depression).
- Currently smoking or using illegal substances.
- Receipt of tetanus-diphtheria toxoid immunization within the past 2 years.
- Receipt of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine absorbed (Tdap) immunization ever.

Yet, the Tdap vaccine is recommended for all women during every pregnancy, including those with conditions that are covered in the exclusion criteria for the clinical trial.

Closing research gaps prior to pregnant women inclusion in clinical trials.

Given the acknowledged scientific research deficits, and lack of evidence to support the current off label use of vaccines during pregnancy, the draft document for industry would greatly benefit from inclusion of metrics specific to vaccines. There is urgent need to better understand the biological mechanisms of adverse responses to vaccination, high risk factors that make some individuals more susceptible to vaccine injury and death, and whether inducing inflammatory responses to acquire artificial active immunity by atypically manipulating the immune systems of pregnant women contributes to poor health outcomes in pregnant women and their fetuses or their infants born live.

This is especially important given the high infant mortality and rising maternal mortality rate in the U.S. and in light of increasing vaccination rates among pregnant women, together with the

21st Century Cures Act's indemnification of vaccine manufacturers for liability when pregnant women or their infants are harmed by vaccines administered during pregnancy.

NVIC strongly reiterates the need for transparency regarding the inclusion of vaccines as biological products in this draft document, if the intent of this guidance is to apply to vaccines. Such integration should include the requirements similarly noted for drugs, e.g. "adequate nonclinical" studies, including studies on pregnant animals. Similarly, such guidance should restrict enrollment of pregnant women into vaccine clinical trials until nonclinical reproductive and developmental toxicology studies are completed, as noted in the guidance document for drugs and timing of enrollment. These additions to the guidance document would assist in closing research gaps noted on vaccine product inserts, the prevention of vaccine injuries and deaths, and align with the precautionary principle and informed consent ethic.

Respectfully submitted,



Barbara Loe Fisher
Co-founder & President



Theresa K. Wrangham
Executive Director

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