FDA U.S. FOOD & DRUG ADMINISTRATION

October 1, 2018

Ralph Fucetola, J.D.
Natural Solutions Foundation
58 Plotts Road
Newton, NJ 07860

Re: Docket Numbers FDA-2009-P-0418
FDA-2010-P-0651

Dear Mr. Fucetola and Others:

This letter responds to your citizen petitions filed on August 31, 2009 (2009 Petition), and December 22, 2010 (2010 Petition), submitted to the Food and Drug Administration (FDA or Agency or we) on behalf of Natural Solutions Foundation and others.[1] In your petitions, you request that FDA take numerous actions in connection with the pandemic influenza vaccines (Influenza A (H1N1) 2009 Monovalent Vaccine) (hereinafter 2009 H1N1 vaccine) and the 2010/2011 seasonal influenza virus vaccines (hereinafter 2010/2011 seasonal vaccine), which contain Influenza A (H1N1) 2009 hemagglutinin antigen.

We note that your petitions contain a number of requests that are either moot or not applicable to FDA. Nonetheless, to the extent they are applicable to the Agency, we have carefully considered them. We appreciate your concern for the safety, purity and potency of the monovalent vaccines against the pandemic Influenza A (H1N1) 2009 influenza virus and of the 2010/2011 seasonal vaccine which contains pandemic H1N1 virus hemagglutinin antigen, referred to in your correspondence as "the Vaccines."[2]

After review and consideration, we find that some portions of the petitions have already been granted in part and deny the remainder of the requests in the petitions for the reasons set forth below.

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[1] FDA previously sent you interim responses to your petitions dated February 16, 2010, and June 7, 2011, respectively. We note that the August 2009 petition includes Appendix A with additional signatories; however, the December 2010 petition does not include this appendix.

[2] For ease of reference, when discussing both the pandemic (H1N1) 2009 influenza virus and the 2010-2011 formulation of the seasonal influenza virus vaccines, we will refer to them collectively as "the Vaccines."

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DISCUSSION

I. The Dangers of Influenza

Influenza, in both its seasonal and pandemic forms, is an ongoing public health concern. It has been associated with 3,000 to nearly 50,000 deaths each year in the United States (U.S.) in recent decades, according to the Department of Health and Human Services' (HHS) Centers for Disease Control and Prevention (CDC).[3] We are incorporating by reference the response we issued in a citizen petition from the Coalition for Mercury-free Drugs (CoMeD) dated August 10, 2007, to which we issued a response on November 21, 2008.[4] In the 2008 CoMeD response (CoMed Response), we provided an explanation of the dangers of influenza. Please see the CoMeD Response on pages 27-33.

II. Statutory and Regulatory Framework

Congress has set out the clear statutory requirement that every vaccine approval be based on a demonstration that the product is safe, pure, and potent.[5] The products at issue were shown through rigorous scientific studies to meet this requirement prior to licensure.[6] Regarding the statutory and regulatory framework governing FDA's approval of these products, we are incorporating by reference the responses that we provided in the CoMeD Response. Please see the CoMeD Response on pages 3-4.

III. H1N1 Background Information

The 2009 H1N1 pandemic influenza virus emerged in the spring of 2009, and was serious enough to prompt FDA and others to take steps to ensure the development of vaccines.[7] Although the 2009 H1N1 virus had not been previously identified, it belongs to an influenza A subtype with which FDA was familiar. Specifically, it belonged to the same influenza A H1N1 subtype as that presented in the then-currently licensed seasonal trivalent (meaning that they contained two different influenza A subtypes and an influenza B type) influenza vaccines.[8] Notably, the 2009 H1N1 virus was identified in March 2009, after the World Health Organization (WHO) and the Vaccines and Related

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[3] CDC, "Estimates of Deaths Associated with Seasonal Influenza-United States, 1976-2007." Available at https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5933a1.htm.

[4] The CoMed Response can be found under Docket Number FDA-2007-P-0232 at www.regulations.gov; a copy is also included as an attachment to this response.

[5] 42 U.S.C. § 262 (a)(2)(C)(i)(I).

[6] Information on the Influenza A (H1N1) 2009 monovalent vaccines is available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm and http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm182335.htm.

[7] The designation of the 2009 H1N1 virus as "pandemic" is derived from the WHO name for the virus (pandemic (H1N1) 2009). On June 11, 2009, the WHO declared a pandemic alert from phase 5 to phase 6, reflecting the human-to-human spread of the virus into at least two countries in one WHO region as well as community level outbreaks in at least one other country in a different WHO region.

[8] Defendant's Memorandum in Support of Motion to Dismiss and in Opposition to Plaintiffs' Motion for Preliminary Injunction at 4, Null et al. v. U.S. Food and Drug Administration, D. D.C., Civil Action No. 09-1924 (RBW).

Biological Products Advisory Committee (VRBPAC) each met in February 2009 to recommend appropriate strains to include in the seasonal vaccines for the northern hemisphere and the U.S., respectively.[9]

The regulatory pathway to licensure for the monovalent (meaning that it contained only the H1N1 subtype) influenza A (H1N1) 2009 vaccines was discussed in an open meeting of FDA's VRBPAC on July 23, 2009.[10] We note that the meeting was announced in the Federal Register, and background materials were made available before the meeting.[11] At the meeting, FDA presented its licensing pathway for approval of the 2009 H1N1 monovalent vaccines for discussion: licensure as a biologics license application (BLA) strain change supplement to the manufacturers' existing licenses. This approach is consistent with licensure of yearly seasonal influenza vaccines by manufacturers with existing BLAs for seasonal vaccines and relies on existing data in the BLA. The Committee unanimously agreed with FDA regarding this regulatory pathway and agreed that it best addressed the urgent public health need for a pandemic (H1N1) 2009 influenza vaccine, and was consistent with previous FDA regulatory decisions concerning influenza vaccines.[12] The Influenza A (H1N1) 2009 Monovalent vaccines were approved in the fall of 2009.

IV. Procedural Posture

As discussed above, your first petition was filed on August 31, 2009, seeking a temporary stay of all then-pending approvals for vaccines to prevent influenza disease caused by pandemic (H1N1) 2009 virus. In that petition, you asserted that FDA was treating the vaccine approvals on an emergency basis without requiring science-based safety or efficacy testing, and that such vaccines would have "dangerous adjuvants." (2009 Petition at 2). You requested that FDA accept public comment on the approval process for the vaccines, require strong warnings on the labeling, and develop a process for individuals to opt out of mandatory vaccination programs. *Id.* at 10.[13] On October 9, 2009, approximately six weeks after filing the 2009 Petition, two of the named signatories to the 2009 Petition, Mr. Gary Null, Ph.D. and Natural Solutions Foundation, filed a complaint in the U. S. District Court for the District of Columbia, seeking

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[9] The WHO convenes technical meetings in February and September of each year to recommend the composition of influenza vaccines for the northern and southern hemispheres, respectively. *See, for example*, http://www.who.int/influenza/vaccines/virus/recommendations/2014_south/en/. The VRBPAC meets yearly to recommend the composition of influenza vaccines for the U.S. *See, for example,* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/default.htm.

[10] *See* July 23, 2009 Advisory Committee transcripts. Available at https://wayback.archive-it.org/7993/20170111231309/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129568.htm.

[11] *See* meeting notice in the Federal Register at 74 FR 32614, Wednesday, July 8, 2009.

[12] *See* July 23, 2009 Advisory Committee transcripts, at 163-174. Available at https://wayback.archive-it.org/7993/20170111231309/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129568.htm.

[13] 21 CFR 10.30(e)(2).

substantially the same relief as sought in the 2009 Petition. The court dismissed the case for lack of standing on November 10, 2009.

On February 16, 2010, FDA sent you an interim response to your petition, noting that the FDA had not yet completed its response to the issues raised in your petition. On December 22, 2010, you filed a substantially similar petition seeking mostly the same relief; however, you also included a discussion of the 2010/2011 seasonal vaccine in the 2010 Petition. On June 7, 2011, FDA sent you an interim response to the 2010 Petition.

V. Relief Sought

As we understand your petitions, you make a number of assertions regarding safety and you seek a number of actions from FDA and CDC in response to your assertions regarding the Vaccines.

In both petitions, you contend that FDA and CDC are required to "reject" approval for the Vaccines because the Vaccines are "more likely than not" to have adverse effects on the vaccine recipients' immune and neurological systems.[14]

Moreover, as set forth in the section entitled "Redress Sought," of the August 31, 2009, petition, you seek the following actions to be taken:

1. "[A]n emergency Temporary Stay of the pending Vaccine approval applications. Petitioners request a Public Hearing. Petitioners are in imminent peril of irreparable harm if the Temporary Stay is not granted immediately."

2. You ask FDA and/or CDC to include additional warnings on vaccine labels and engage in a public information campaign regarding vaccine risks.

3. Furthermore, you ask FDA and/or CDC to recommend to all "implementing agencies," such as the State Departments of Health not to require mandatory vaccination for any reason."[15]

4. You further ask FDA and/or CDC to "...recommend voluntary Self-Shielding at home in preference to vaccination or removal to FEMA [Federal Emergency Management Agency] or other relocation facilities in the event of a Declared Pandemic Emergency."[16]

5. Finally, in your December 22, 2010 petition, you request that FDA suspend the approvals for the 2010/2011 seasonal influenza vaccines based on adverse

[14] 2010 Petition at page 6, and 2009 Petition at page 5.
[15] *Id.*
[16] *Id.*

events, including miscarriages, reported to the Vaccine Adverse Event Reporting System (VAERS).[17]

We note that the redress sought, while not identical, is similar in both petitions. Given the Agency's understanding of the requests in the petitions, and for the reasons set forth below, we deny the petitions to the extent your requests are relevant to FDA. We note that, as a general matter, some of your requests are moot because H1N1 monovalent vaccines for 2009 were approved on September 15, 2009 and November 10, 2009, and because the April 26, 2009 declaration of a public health emergency by the Department of Health and Human Services (DHHS) in response to H1N1 influenza expired on June 23, 2010. With respect to the remaining requests, we address them below.

VI. Response to Relief Sought

A. The Vaccines Were Shown to be Safe Prior to Licensure

In the petitions, you question the safety of the Vaccines and have requested that FDA grant a temporary stay of the approval of the 2009 H1N1 vaccine applications and the 2010/2011 seasonal vaccine applications. We deny your requests for a temporary stay with respect to both applications because you have provided no scientific evidence that supports any of your assertions related to safety, and because FDA is not aware of any evidence that supports your assertions. You also request a public hearing. We deny your request for an additional public hearing on FDA's evaluation and approval of the Vaccines because FDA approved the Vaccines based upon a showing that they were safe, pure, and potent in accordance with 42 U.S.C. § 262(a)(2)(C)(i)(I).

For example, we note that you have provided no evidence to support your assertions that FDA approved the Vaccines even though there was not "even minimal science-based safety testing or testing for clinical efficacy in preventing disease." As discussed above, with respect to the 2009 H1N1 vaccine, in approving the vaccines, FDA relied on the extrapolation of safety, purity and potency from clinical data included in the approved license applications and from FDA's post-marketing experience with prior years' seasonal influenza vaccines, as well as the assurance that the 2009 H1N1 vaccine was to be manufactured using the licensed process.[18] As for the 2010/2011 seasonal vaccines, FDA relied on the same criteria and approval process to ensure safety, purity and potency. In both cases, FDA's determinations that the vaccines at issue satisfied the regulatory approval requirements were based on decades of experience in evaluating the safety, purity and potency of influenza vaccines.

Your assertions that the Vaccines included squalene are incorrect. The licensed 2009 H1N1 vaccine and the licensed 2010/2011 seasonal vaccines did not contain any adjuvants, and specifically did not contain squalene, as was evident from the package inserts, which were posted on FDA's website. Examples of package inserts from a

[17] 2010 Petition at 2.
[18] For more information, we refer you to the Memorandum In Support of Motion to Dismiss at 8-9.

licensed 2009 H1N1 vaccine and a licensed 2010/2011 seasonal vaccine are attached to this response.

With respect to your assertions regarding mercury, we are incorporating by reference the responses that we provided to the CoMeD Response, in which we addressed the concerns that you raised.

Finally, with respect to your claims regarding possible adverse effects on vaccine recipients, you have provided no evidence to support your assertions. Nonetheless, because of the seriousness of these assertions, we believe it is important to address them in our response. As described above, the safety, purity and potency of the Vaccines was based on clinical data included in the approved license applications and on post-marketing experience with preceding seasonal vaccines, which was evaluated during post marketing surveillance after licensure. Change in the influenza virus antigens requires annual assessment of influenza vaccine strains and annual administration of seasonal influenza vaccine. Each new inactivated seasonal influenza vaccine made by currently licensed influenza vaccine manufacturers is licensed without submission to the BLA of additional clinical data specific for the new strain(s). For live attenuated influenza vaccines FDA does receive limited safety data which is evaluated by the agency before approval annually. Safety and effectiveness of each new seasonal inactivated vaccine are extrapolated from data included in the approved license application as well as data from post-marketing experience with prior years' seasonal vaccines. FDA regulations define safety as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking in consideration the character of the product in relation to the condition of the recipient at the time."[19] When applying the regulatory standards, FDA weighs a vaccine's risks against its benefits to determine whether the vaccine is safe. FDA applies this standard to all vaccines, including the 2009 H1N1 vaccine and the 2010/2011 seasonal vaccine. Furthermore, after approval, FDA and CDC closely monitored the safety of the 2009 H1N1 vaccine and the 2010/2011 seasonal vaccine. Please see section E. below for a detailed discussion.

B. Warnings to the Public

1. Public Comments

You have requested a "public hearing." As noted in Section III, the Agency held an Advisory Committee meeting on July 23, 2009 regarding clinical trials to support the use of vaccines against the 2009 H1N1 influenza virus, and the public had an opportunity to comment on the monovalent 2009 H1N1 vaccines.[20] We note that FDA is committed to transparency and provides public notification of opportunities

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[19] 21 CFR 600.3(p).

[20] *See* https://wayback.archive-it.org/7993/20170111231309/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm129568.htm.

for all members of the public to comment and provide data and information at these meetings.[21] We deny your request for an additional public hearing on FDA's evaluation and approval of the Vaccines for the reasons discussed in Section VI. A above and because the public had the opportunity to comment and provide data at the July 23, 2009 Advisory Committee meeting.

2. Public Information Campaign

You have requested that FDA and/or CDC "engage in a vigorous public information campaign regarding vaccine risks." We agree that transparency and data sharing are of fundamental importance to our ability to achieve our strategic goals of advancing public health. Consistent with these goals, we note that the Agency provided information to the public about the 2009 H1N1 vaccines, including information regarding the ingredients in them.[22] Information regarding the 2010/2011 seasonal vaccines was also available in the package inserts, a copy of which is attached to this response. That information was also available on the FDA website when they were approved. In addition, since the submission of your petitions, HHS has also launched the following website: http://www.flu.gov (now https://www.vaccines.gov), as a way to disseminate information to the public regarding vaccines and vaccine safety.

With respect to information regarding vaccine recommendations, your request is more appropriately directed to CDC, as CDC, taking into account advice from its Advisory Committee on Immunization Practices (ACIP), provides annual recommendations for the prevention and control of influenza, which include recommendations as to who should be vaccinated during a specific influenza season and the timing of such vaccination.[23] Nonetheless, we have carefully considered your request as it pertains to FDA. We have already granted your request, in part, as FDA has already provided, and will continue to provide, information to the public about vaccines in general and influenza vaccines in particular.

3. Warnings on Labels

In response to your request for specific warnings in addition to those that already are on the label, the statements you have requested FDA to require on the warning label are each false. As discussed above, each vaccine has been found to be safe, pure and potent. None of the ingredients have been "previously rejected."[24] Accordingly, we deny your request for these warnings. Please note that regulations require that labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal

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[21] http://www.gpo.gov/fdsys/pkg/FR-2009-07-08/html/E9-16099.htm, *see* footnote 11 above.
[22] *See, for example,* http://www.fda.gov/biologicsbloodvaccines/vaccines/questionsaboutvaccines/ucm182335.htm. *See* http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm186102.htm for specific discussion of monovalent influenza A (H1N1) 2009 vaccine ingredients.
[23] *See* https://www.cdc.gov/flu/pastseasons/1213season.htm.
[24] 2010 Petition at 5.

relationship need not have been definitively established."[25] You have not provided any scientific evidence of a possible plausible relationship between a clinically significant hazard and the Vaccines that would support inclusion of these specific warnings in labeling.

4. National Vaccine Injury Compensation Program

Finally, with respect to your assertion that "the National Vaccine Injury Compensation Program does not provide for possible compensation to victims of the Vaccines,"[26] we agree that the National Vaccine Injury Compensation Program, which is designed to cover certain adverse reactions to specific vaccines, does not currently include either the 2009 H1N1 vaccine or the 2010/2011 seasonal vaccine. However, the statement in your requested warning language that "should the recipient experience an adverse event or death from the vaccine, the vaccine manufacturers, government and government agencies have no liability"[27] is inaccurate. The National Childhood Vaccine Injury Act of 1986 does not prohibit an individual from privately seeking compensation for injury resulting from either the 2009 H1N1 vaccine or the 2010/2011 seasonal vaccine but does not provide for compensation under the National Vaccine Injury Compensation Program. Therefore, we deny your request.

C. Required Vaccination

You request that the Vaccines "not be subject to any legal mandate"[28] that would require a person to be vaccinated in order to receive government services, be employed, travel, or attend public events. We note that, although FDA properly approved the Vaccines, it does not control the policies of state or other authorities related to vaccination or of private employers as to vaccination of employees as a condition of employment. Therefore, FDA is denying this portion of your petition because it does not raise an issue upon which FDA can act.

D. Self Shielding

You have requested that FDA and/or CDC "recommend voluntary Self-Shielding at home in preference to vaccination."[29] As mentioned above, HHS launched a website, http://www.flu.gov (now https://www.vaccines.gov), which specifically states "[i]f you have been diagnosed with the flu, you should **stay home** and follow your health care provider's recommendations."[30] We note that CDC is the appropriate agency to make recommendations as to voluntary isolation when sick and that CDC does, in fact, recommend that individuals voluntarily stay home from work and school if they become

[25] 21 CFR 201.57(c)(6)(i).
[26] 2009 Petition at 3.
[27] 2009 Petition at 3.
[28] 2009 Petition at 3.
[29] 2009 Petition at 3 and 2010 Petition at 5.
[30] *See* print out of page attached to this response (emphasis in the original).

infected with influenza in order to prevent spreading the disease to others.[31] Therefore, FDA is denying this portion of your petition because it does not raise an issue upon which FDA can act.

E. Monovalent Influenza A (H1N1) 2009 and 2010/2011 Seasonal Influenza Vaccines Safety Surveillance

Your petition describes your concerns about the safety of the 2009 H1N1 vaccine. Your petition also requests that we suspend approval of the 2010/2011 seasonal vaccine due to adverse events, including miscarriages, reported to VAERS. In response to these concerns, we provide a summary of the safety surveillance conducted during the 2009-2010 influenza season, during which the 2009 H1N1 vaccine was used, and subsequent influenza seasons, including the 2010/2011 season, when the 2010/2011 seasonal vaccine was used. A careful evaluation of these data reveal that the safety of the Vaccines has been comparable to the safety of influenza vaccines used in prior seasons. Substantial risks associated with the Vaccines have not been identified.

Monitoring the safety of influenza vaccines, including the 2009 H1N1 vaccine, is a responsibility that FDA shares with the CDC.[32,33,34] Through a network of diverse, yet integrated, surveillance activities, FDA and CDC monitor adverse events and study health outcomes following influenza vaccination in the U.S. on an ongoing basis during each influenza season.

The details of adverse event monitoring for the 2009 H1N1 vaccine, conducted as part of the federal response to the 2009 influenza pandemic, are available in a document entitled "Immunization-Safety Monitoring Systems for the 2009 H1N1 Monovalent Influenza Vaccination Program" by Salmon D, et al.[35] Many of these systems were in place for years or decades prior to 2009, and continue to be used for safety evaluation each year. The safety of the Vaccines, as assessed through these systems, has been comparable to vaccines administered in previous influenza vaccine seasons, and substantial risks associated with these vaccines have not been identified.[36] In aggregate, these systems facilitate three key components of influenza vaccine safety surveillance: safety signal

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[31] *See* http://www.cdc.gov/flu/protect/habits/index.htm.
[32] Information on H1N1 vaccine safety monitoring maintained by the FDA is available at https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/vaccinesafety/ucm298181.pdf.
[33] Information on the safety and monitoring of the H1N1 flu vaccines maintained by the CDC is available at http://www.cdc.gov/h1n1flu/vaccination/vaccine_safety.htm.
[34] *See* http://www.cdc.gov/vaccinesafety/Vaccine_Monitoring/Index.html, *see also* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/.
[35] *Pediatrics*, 2011;127;S78 (hereinafter "Salmon article"). *See also* Vellozzi C, et al., Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009 January 31, 2010. *Vaccine*, 2010 Oct 21;28(45):7248 55. Epub 2010 Sep 16 (hereinafter "Vellozzi article").
[36] *Id.*

detection; surveillance for pre-specified adverse events of interest; and safety signal evaluation.[37] We address each of these components below.

1. Safety Signal Detection

Vaccine Adverse Event Reporting System (VAERS)[38]

Co-managed by CDC and FDA, VAERS is a spontaneous reporting system established in 1990, which allows healthcare providers and patients to report adverse events suspected to be associated with the use of vaccines.[39] Serious adverse events are defined as adverse events that result in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. VAERS can assess early indicators of a possible vaccine safety problem that present as new or unusual adverse events or patterns of reports.[40]

FDA and CDC Medical Officers and epidemiologists review VAERS reports and routinely evaluate VAERS data to look for changes in reporting patterns, and the VAERS program obtains follow-up information, including relevant medical records, for further evaluation of serious reported events.[41] Data mining is a process that involves the use of software programs to identify adverse events that are disproportionally reported for a particular vaccine compared to other licensed vaccines.[42] Data mining provides an automated method to screen and analyze the large VAERS database for adverse events that have been reported unusually frequently for a particular vaccine, thus complementing review of VAERS records. New safety signals for influenza vaccines identified through VAERS can be evaluated in controlled epidemiologic studies to verify if the signal is caused by administration of the vaccine.

It is important to note that VAERS is a passive surveillance system; that is, VAERS accepts reports of any adverse events following vaccination, be they coincidental or truly caused by a vaccine. The report of an adverse event to VAERS does not constitute proof that the vaccine caused the event.[43] Likewise, the number of events that patients, family members, health care providers, or others report to VAERS can be increased by factors that are unrelated to whether or not the vaccine causes the event, such as an increase in

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[37] *See* Varricchio F, et al., Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatric Infectious Disease* 2004 Apr 23(4):287-94 (hereinafter "Varricchio article").
[38] The VAERS website is available at http://vaers.hhs.gov/index.
[39] Varricchio article at 287-88 and Salmon article.
[40] Salmon article at S81.
[41] Vellozzi article at 7248, *see also* http://www.cdc.gov/vaccinesafety/Activities/vaers.html.
[42] Vellozzi article at 7249.
[43] Varricchio article at 288-90, *see also* http://www.cdc.gov/vaccinesafety/Activities/vaers.html.

the number of exposures (vaccinations) or increased media attention or other public awareness about a potential adverse event (i.e., stimulated reporting). These circumstances can lead to an increase in the crude number of adverse events reported to VAERS when there has not actually been an increase in the rate of the adverse event in the vaccinated population. For example, the 2009 H1N1 influenza vaccination was specifically recommended for the high-risk group of pregnant women (increased number of exposures) and those who received the vaccine, as well as their health care providers, were more aware of the need to report adverse events to VAERS during this time (stimulated reporting). Increased numbers of women vaccinated in this group (who already have a baseline rate of spontaneous abortion), as well as the increased awareness and attention to adverse event reporting, are likely explanations for the increase in the number of miscarriages reported to VAERS during the 2009-2010 influenza season compared to previous influenza seasons.

As mentioned above, for the 2009 H1N1 vaccination program, CDC additionally conducted educational outreach about VAERS to healthcare providers, state vaccine safety coordinators, and the public to encourage reporting and improve the quality of the information provided. With respect to VAERS' monitoring of the Vaccines, FDA and CDC staff reviewed VAERS reports and sought medical records for all reports coded as serious and for reports suggesting Guillain-Barré Syndrome (GBS) and other events of interest.[44] A study conducted by FDA and CDC of adverse events reported to VAERS from October 1, 2009, through January 31, 2010, concluded that the safety profile of the 2009 H1N1 vaccine was consistent with those of other seasonal influenza vaccines.[45] The proportion of serious reports received following the 2009 H1N1 vaccine was also generally consistent with the pattern of VAERS reporting for seasonal influenza vaccines over the last five years. Other studies have examined VAERS reports for influenza vaccines over several influenza seasons, including the 2009-2010, 2010-2011, and subsequent seasons.[46] The frequency and types of adverse events reported for the 2009/2010 and 2010/2011 seasons were similar to those for previous influenza vaccine seasons. These studies did not identify any substantial risks associated with the Vaccines.

2. Surveillance for pre-specified adverse events of interest

Each season, both FDA and CDC use large electronic healthcare databases to monitor pre-specified adverse events of special interest. Certain events could be chosen as events of special interest due to a previous association with the vaccine, such as Guillan Barre Syndrome which was observed with increased frequency after the 1976 Swine flu

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[44] Vellozzi article at 7248-49.
[45] *Id* at 7254.
[46] Haber, P. et al., Post-licensure surveillance of trivalent live attenuated influenza vaccine in adults, United States, Vaccine Adverse Event Reporting System (VAERS), July 2005-June 2013. *Vaccine*, 2014 Nov 12;32(48):6499-504. doi: 10.1016/j.vaccine.2014.09.018. Epub 2014 Sep 22; and Halsey, N.A. et al., Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS. *Vaccine*, 2013 Dec 9;31(51):6107-12. doi: 10.1016/j.vaccine.2013.09.066. Epub 2013 Oct 8.

vaccine, or to further monitor an event that was noted in spontaneous reports submitted to VAERS during prior vaccination seasons.

Your petition states that the "British Neurological Surveillance Unit" "alerted its members to be on the alert for an up to 8-fold increase in [GBS] due to the Vaccines that are the subject of this Petition".[47] The 2009 on-line report cited in your petition describes a letter from the Health Protection Agency in the United Kingdom. According to the article, the letter refers to the risk observed after the 1976 Swine flu vaccination and asks physicians in the UK to monitor for GBS during the 2009 vaccination season. Similar increases in GBS risk have not been identified in association with the 2009 H1N1 vaccination, the 2010-2011 seasonal influenza vaccination, or with any other seasonal influenza vaccination. We describe below several methods by which CDC and FDA monitor for GBS and other adverse events of interest.

a. Centers for Medicare and Medicaid Services (CMS) Claims Database

Since the 2008-2009 influenza season, FDA and CMS have used healthcare claims data for U.S. Medicare beneficiaries to monitor hospitalizations and diagnosis codes for GBS after influenza vaccinations. This adverse event surveillance provides timely analysis of GBS rates among flu vaccinees from a population of approximately 35 million individuals (vaccinated and unvaccinated) as of the 2009-2010 flu season).[48] In this near real-time surveillance, GBS rates among flu vaccinees are calculated weekly. Each week the GBS rate is statistically compared to GBS rates over several preceding influenza seasons to assess if it is statistically elevated. During the 2009-2010 flu season, this weekly surveillance compared the GBS rate after 2009 H1N1 vaccination to the GBS rates over the preceding five influenza seasons, and it also compared the GBS rate after 2009-2010 seasonal influenza vaccination to the GBS rates over the preceding five influenza seasons.[49] No safety signal was detected in either group; in other words, no increased rate of GBS was noted when the 2009 H1N1 vaccinees were compared with the historical control group, or when the 2009-2010 seasonal influenza vaccinees were compared with the historical control group.

In an associated study using CMS data, described in the Polakowski article, FDA compared the rate of GBS in the 1-42 day period following 2009 H1N1 vaccination to the GBS rate in the same vaccinees during the 50-119 days after vaccination (i.e., unvaccinated control period). The rate in the 1-42 days after vaccination was only slightly higher than the control period, with the possible risk attributable to vaccination being 2.84 cases per million vaccinations (95% confidence interval 0.21, 5.48). This potential increase in risk is far lower than the potential rate of GBS observed after the

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[47] 2009 Petition at page 2.

[48] Polakowski, L.L., et. al., Chart-confirmed Guillain-Barre syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009-2010. *Am J Epidemiol*. 2013 Sep 15;178(6):962-73, 962-63. doi: 10.1093/aje/kwt051. Epub 2013 May 6 (hereinafter Polakowski article).

[49] Burwen, D.R., et. al., Surveillance for Guillain-Barré syndrome after influenza vaccination among the Medicare population, 2009-2010. Am J Public Health. 2012 Oct;102(10):1921-7. Epub 2012 Feb 16 (hereinafter Burwen article).

1976 swine flu vaccine and consistent with the increase in GBS risk (1-2 cases per million vaccinations) listed in the package insert of influenza vaccines. When the authors applied a stricter case definition for confirming GBS diagnosis, no elevated risk was found after 2009 H1N1 vaccine.

b. Vaccine Safety Datalink (VSD)

Established in 1990, VSD is a large linked database of nine U.S. healthcare organizations that cover about 9 million people, or 3% of the U.S. population.[50] VSD uses demographic and vaccination data linked to diagnoses from medical encounters to study vaccine safety questions or concerns raised from the medical literature and reports to VAERS.[51] The VSD Rapid Cycle Analysis uses vaccination data and diagnoses from medical encounters from participating healthcare organizations that are updated weekly, allowing for evaluation in near real time of rates of adverse events in people who have received a vaccine compared to a similar group of people who have not received the vaccine.[52] This surveillance includes 4-5 selected adverse event types, including GBS, each flu season.[53] Weekly surveillance found no major safety problems following the 2009 H1N1 or 2010/2011 seasonal influenza vaccines.[54]

c. CDC's Emerging Infections Program (EIP)

The Emerging Infections Program (EIP) at CDC is an established collaboration of state health departments and academic centers in 10 states, covering approximately 45 million U.S. residents, that conducts active surveillance of pre-specified health outcomes.[55] In October 2009, EIP began active surveillance to assess the risk of GBS after 2009 H1N1 vaccination. Preliminary results through March 2010 showed a slightly elevated GBS risk among those receiving 2009 H1N1 vaccination (approximately 1.8 times greater than the risk among similar unvaccinated individuals).[56] This finding prompted a meta-analysis that combined end-of-season data across multiple U.S. vaccine safety

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[50] Salmon article at S80.
[51] McNeil, M.M., et. al., The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. *Vaccine*, 2014 Sep 22;32(42):5390-8. doi: 10.1016/j.vaccine.2014.07.073. Epub 2014 Aug 6 (hereinafter McNeil article); Salmon article.
[52] Greene, S.K., et. al., Near Real-Time Surveillance for Influenza Vaccine Safety: Proof-of-Concept in the Vaccine Safety Datalink Project. *Am. J. Epidemiol.* (2010) 171 (2): 177-188; *see also* http://www.cdc.gov/vaccinesafety/Activities/vsd.html.
[53] Kawai, A.T., et. al., Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barré syndrome, encephalitis, or anaphylaxis in the 2012-2013 season. *Pharmacoepidemiol Drug Saf.*, 2014 May;23(5):548-53. doi: 10.1002/pds.3575. Epub 2014 Feb 4 (hereinafter Kawai article); McNeil article.
[54] Lee, G.M., H1N1 and seasonal influenza vaccine safety in the Vaccine Safety Datalink project. *Am J Prev Med.*, 2011 Aug;41(2):121-8. doi: 10.1016/j.amepre.2011.04.004; McNeil article, Kawai article.
[55] CDC, "Preliminary Results: Surveillance for Guillain-Barré Syndrome After Receipt of Influenza A (H1N1) 2009 Monovalent Vaccine --- United States, 2009—2010." Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5921a3.htm; MMWR Weekly Report, June 4, 2010 / 59(21);657-61.
[56] *Id.*

surveillance systems to more comprehensively evaluate the risk of GBS following 2009 H1N1 vaccination.[57] This meta-analysis, which analyzed data gathered by EIP, PRISM, Medicare, VSD, Department of Defense, and Department of Veterans Affairs, concluded that the risk of GBS was consistent with previous estimates of GBS after seasonal influenza vaccination. The meta-analysis reported that the risk of GBS following vaccination translated to an increase of about 1.6 cases of GBS per million vaccinated persons. This meta-analysis is described further in section E.3 Safety Signal Evaluation.

d. Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

The PRISM system combines vaccine exposure data from state and local immunization information systems with claims data from four large health plans with 38 million members.[58] During the 2009 influenza H1N1 pandemic, this system enabled the assessment of 14 key health outcomes among 2.6 million people who had received the 2009 H1N1 vaccine.[59] PRISM data were analyzed at the end of the season and found an elevated, but not statistically significant, risk of GBS after 2009 H1N1 vaccination. Because of the lack of statistical significance, the observed higher rate of GBS after vaccination may not represent any increased risk from the vaccine, but even if true, the increase observed equates to approximately 2-3 cases of GBS per million vaccinations. The risk of other health outcomes of interest were generally not significantly elevated after 2009 H1N1 vaccination.[60]

e. Other relevant healthcare database surveillance

Another study, conducted by CDC, used healthcare claims data from a large health insurer representing approximately 12 million people to evaluate selected health outcomes following influenza vaccination in the 2009-2010 and 2010-2011 influenza seasons.[61] This study did not find any increased risk for the selected health outcomes following over 900,000 seasonal influenza vaccine doses and over 500,000 H1N1 vaccine doses administered in the 2009/2010 season, and over 1 million seasonal influenza vaccine doses in the 2010/2011 season.[62]

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[57] Salmon, D.A., et. al., Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. *Lancet*, 2013 Apr 27;381(9876):1461-8. doi: 10.1016/S0140-6736(12)62189-8. Epub 2013 Mar 13 (hereinafter Salmon *Lancet* article); *see also* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0602a1.htm.

[58] Baker, M., et. al., Post-licensure rapid immunization safety monitoring program (PRISM) data characterization. *Vaccine*, 2013 Dec 30;31 Suppl 10:K98-112. doi: 10.1016/j.vaccine.2013.04.088; Nguyen M., et. al., The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring program: strengthening the federal vaccine safety enterprise. *Pharmacoepidemiol Drug Saf.* 2012 Jan;21 Suppl 1:291-7. doi: 10.1002/pds.2323; *see also* http://mini-sentinel.org/about_us/default.aspx.

[59] Yih, W.K., et. al., Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. *Am J Epidemiol.* 2012 Jun 1;175(11):1120-8. doi: 10.1093/aje/kws197. Epub 2012 May 11.

[60] *Id.*

[61] McCarthy, N.L., et. at., Evaluating the safety of influenza vaccine using a claims-based health system. *Vaccine*, 2013 Dec 5;31(50):5975-82. doi: 10.1016/j.vaccine.2013.10.031. Epub 2013 Oct 19.

[62] *Id.*

3. Safety Signal Evaluation

Regarding the safety of influenza vaccines in pregnant women, we are incorporating by reference the responses that we provided in the CoMeD Response into this discussion section. Please see the CoMeD Response, pages 31.

As described above, FDA, CDC, and CMS can use three large data sources to evaluate potential safety signals through controlled epidemiologic studies. These studies can determine if an observed safety signal reflects a true association between the influenza vaccine and the adverse event, and they can determine the magnitude of the association. The VSD surveillance using Rapid Cycle Analysis and the EIP active surveillance system were used during the 2009 pandemic to monitor the occurrence of selected adverse events of interest, including GBS, and the CMS active surveillance system specifically monitored occurrence of GBS.[63] VSD[64] and PRISM[65] were used to further evaluate signals of possible association between influenza vaccines and selected adverse events.

An end-of-season analysis that assessed the association between GBS and 2009 H1N1 vaccination among Medicare beneficiaries was also conducted as part of a meta-analysis that combined data from multiple U.S. vaccine safety surveillance systems. In the Medicare end-of-season analysis, GBS cases identified in healthcare claims data were confirmed with medical record review. This analysis compared the rate of GBS within the 6-week period immediately following H1N1 vaccination to a later control period among a large population of vaccinees. The results showed a slightly elevated risk of GBS with 2009 H1N1 vaccination, equating to approximately 2-3 more cases of GBS per million vaccinees in the period following vaccination compared to the control period. However, additional results that used a stricter GBS case definition did not find a statistically different rate of GBS after vaccination. These studies thus found that if there is an increased risk of GBS after H1N1 vaccination, it is similar to the risk observed after influenza vaccination in general and already cited in the package insert for all influenza vaccines (1-2 cases per million vaccinees), and well below that seen with the 1976 swine influenza vaccine (which was 7-8 times greater within the 6 weeks after vaccination).

The above-mentioned findings address your assertion of a potential 8-fold increase in GBS among those vaccinated with the H1N1 influenza vaccine.[66] As already noted,

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[63] Burwen article.

[64] Tse, A., et. at., Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine*, 2012 Mar 2;30(11):2024-31. doi: 10.1016/j.vaccine.2012.01.027; Polakowski article; *see also* http://www.cdc.gov/vaccinesafety/Concerns/FebrileSeizures-archived.html.

[65] Update: FDA Postlicensure Rapid Immunization Safety Monitoring (PRISM) study demonstrates no statistically significant association between Trivalent Inactivated Influenza Vaccine and Febrile Seizures in Children during the 2010-2011 influenza season, May 15, 2014 available at http://wayback.archive-it.org/7993/20170112095640/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm397611.htm.

[66] *See* 2009 Petition at page 2, paragraph 6.

several federal surveillance systems undertook studies or surveillance programs specifically examining the risk of GBS after H1N1 influenza vaccination and each of these systems contributed to a combined meta-analysis of GBS risk following H1N1 vaccination.[67] This meta-analysis,[68] which analyzed data gathered by CDC's Emerging Infections Program (EIP), PRISM, Medicare, VSD, Department of Defense, and Department of Veterans Affairs, concluded that the risk of GBS was consistent with previous estimates of GBS after seasonal influenza vaccination, and this risk was only about one-third as high as the GBS risk observed after the 1976 swine flu vaccination (2.4-fold compared with 7.6-fold).[69] Similar to the findings of the Medicare and PRISM studies discussed above, the meta-analysis reported that the risk of GBS following vaccination translated to an increase of about 1.6 cases per million vaccinated persons. Given the reductions in hospitalizations and deaths due to complications from influenza each year, the small elevated risk of GBS after influenza vaccination in some populations is outweighed by the benefits of vaccination.

CONCLUSION

Influenza vaccination is an important tool and the most effective method for preventing influenza and influenza-related complications. We appreciate the concerns expressed in the petitions as to the safety of the Vaccines. The Agency agrees that it is critical that vaccines be demonstrated to be safe, pure and potent, and that the labeling for vaccines reflect FDA's review of the pertinent scientific evidence and communicate to health care practitioners the Agency's formal, authoritative conclusions regarding the appropriate use of the product. FDA is committed to continuing to work with federal partners to monitor the safety of all vaccines, including those that were approved for the 2009/2010 and 2010/2011 influenza seasons, and to clear communication with the public.[70]

After careful consideration of the issues raised in the petitions, we have determined that FDA has already granted some of your requests, and we deny the remainder of your requests for the reasons explained above to the extent they are applicable to the Agency. FDA's decisions to approve the 2009 H1N1 vaccine and 2010/2011 seasonal vaccine were in accordance with the applicable legal requirements and were based upon the scientific data in each vaccine license application. In addition, the labeling for the Vaccines appropriately communicated to health care providers the risks and benefits associated with these products.

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[67] Salmon *Lancet* article; see also http://www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0602a1.htm.
[68] *Id* at 1461-68.
[69] Salmon *Lancet* article; Polakowski article; and Burwen article.
[70] The FDA press release announcing approval the seasonal vaccines for the 2011-2012 influenza season, which includes the H1N1 flu virus, is available at https://wayback.archive-it.org/7993/20161023133232/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm263319.htm.

Sincerely yours,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Division of Dockets Management

Enclosures:
Coalition for Mercury-free Drugs Citizen Petition Response, FDA-2007-P-0232-0004, Nov. 21, 2008
Package insert for 2009 H1N1 vaccine (Sanofi Pasteur Inc. Influenza A (H1N1) 2009 Monovalent Vaccine, September 10, 2009)
Package insert for 2010/2011 seasonal influenza vaccine (Sanofi Pasteur Inc. Fluzone, July 14, 2010)