

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

GARY NULL <i>et al.</i> ,)	
)	
Plaintiffs,)	
)	
v.)	Civil Action No. 09-1924 (RBW)
)	
U.S. FOOD AND DRUG)	
ADMINISTRATION, <i>et al.</i> ,)	
)	
)	
Defendants.)	
)	

**DEFENDANTS’ MEMORANDUM IN SUPPORT OF MOTION TO DISMISS AND
IN OPPOSITION TO PLAINTIFFS’ MOTION FOR PRELIMINARY INJUNCTION**

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Plaintiffs, who object to a now-suspended New York regulation that would have mandated vaccination for health care personnel, seek to overturn the Food and Drug Administration's ("FDA") approval of the H1N1 ("swine flu") vaccine and thus block its distribution, even as the President has declared a national emergency and countless people throughout the country line up to receive the vaccine. Despite the fact that plaintiffs, who identify themselves as New York health care workers, are no longer required to receive the vaccine, they would nevertheless deny millions of Americans the ability to protect themselves and their families from a dangerous strain of influenza, needlessly exposing them to the risk of serious illness and impeding the efforts of public health officials to battle a worldwide influenza pandemic.

In these circumstances, plaintiffs' motion for preliminary injunction is as irresponsible as it is meritless. Plaintiffs have no standing to maintain this action, given their ability to choose to receive – or not receive – the H1N1 vaccine. Moreover, even if the New York mandatory vaccination regulation were still in effect, any harm that plaintiffs might suffer as a result is attributable to the regulation itself, not to FDA's approval of the vaccine, as this Court has already observed. *See* Scheduling & Show Cause Order at 3. In any event, as plaintiffs' complaint makes clear, plaintiffs' allegations about the vaccine are based less on what FDA actually did – approve the vaccine licenses on the basis of sound scientific evidence – than on plaintiffs' speculative and ill-founded fears about what FDA might possibly do in the future. Plaintiffs' conjecture, however, and their personal objections to the vaccine, do not justify denying its availability to the American public. Given the clear non-justiciability of plaintiffs' claims, and their utter lack of merit, plaintiffs' complaint should be dismissed for lack of jurisdiction and failure to state a claim, and their motion for preliminary relief should be denied without a hearing.

BACKGROUND

I. Statutory and Regulatory Framework

A. Biological Products Licensed by FDA

The Public Health Service Act (“PHSA”), 42 U.S.C. §§ 201, *et seq.*, and the Federal Food, Drug, and Cosmetic Act (“FDCA”), 21 U.S.C. §§ 301, *et seq.*, govern the regulation of biological products in the United States.¹ The PHSA governs licensing of biological products; it grants FDA authority to issue licenses based on a showing that the biological product is “safe, pure, and potent,” 42 U.S.C. § 262(a)(2)(C)(i)(I), and that the facility in which the product is manufactured “meets standards designed to assure that the biological product continues to be safe, pure, and potent.” *Id.* § 262(a)(2)(C)(i)(II). Licenses are issued by FDA upon approval of a “biological license application,” or “BLA.” The PHSA expressly authorizes the Secretary of the Department of Health and Human Services (“HHS”) to “establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.” *Id.* § 262(a)(2)(A). For a BLA, FDA regulations require manufacturers to submit “data derived from non-clinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency.” 21 C.F.R. § 601.2(a).

Biological products, such as vaccines, intended for human use are also “drugs” for purposes of the FDCA, 21 U.S.C. § 321(g)(1)(B), and, FDA is charged with approving drugs that

¹ The PHSA defines biological products as any “virus, therapeutic serum, toxin, antitoxin, vaccine . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.” 42 U.S.C. § 262(i).

are safe, effective, and not misbranded. *See id.* § 355(d);² *see also generally* Procedures for Review of Safety, Effectiveness, and Labeling, 37 Fed. Reg. 16,679, 16,679-80 (Aug. 18, 1972) (explaining the interplay between PHSA and FDCA with respect to biologics); *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 25 (D.D.C. 1996) (discussing FDA regulations for determining safety, purity, and potency under the PHSA).

B. Changes to Approved Licenses for Influenza Vaccines

FDA regulations allow a manufacturer of a product covered by an approved license to make certain changes to that product. 21 C.F.R. § 601.12. Some changes, including those that have substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product, must be approved by the agency prior to distribution, and thus require submission of a supplement to the original BLA. *See* 21 C.F.R. § 601.12(b). Strain changes for seasonal vaccines are considered to be changes to the “Chemistry Manufacturing and Controls” or “CMC” section of the BLA and require FDA approval of a supplement before distribution of the modified product. *See* FDA Approval Memoranda at 6 (attached hereto as Exhibits 1-4); *see also* 21 C.F.R. § 601.12(b)(2)(I), (iv), and (v) (changes relevant to CMC supplements).

² Under the FDCA, as amended in 1962, a drug for human use must be shown to be both safe and effective prior to approval. FDA, by regulation, has interpreted the “potency” requirement for biological products under the PHSA to mean “the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.” 21 C.F.R. § 600.3(s). The potency requirement for approval of biologics is thus comparable to the efficacy requirement for approval of drugs.

II. Factual Background

A. Influenza A (H1N1) 2009 Vaccine

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 a vaccine.³ FDA has extensive experience with influenza vaccines. Before 1978, seasonal influenza vaccines provided protection against one or two virus strains, and were called “monovalent,” or “bivalent,” respectively. *See* FDA Approval Memoranda (Exhibits 1-4) at 4. Since 1978, most seasonal vaccines have been “trivalent,” meaning that they contain two different influenza A subtypes [A (H1N1) and A (H3N2)] and an influenza B type. *Id.* These influenza viruses undergo frequent antigenic change, which necessitates annual reassessment of the optimal strains for inclusion in the seasonal vaccines. The strains contained in the vaccine are those expected to be circulating and to cause disease.

The 2009 H1N1 virus belongs to the same influenza A H1N1 subtype as that present in the currently licensed seasonal trivalent influenza vaccines. *Id.* at 2. In its approval memoranda, FDA characterized the 2009 H1N1 virus:

Although pandemic (H1N1) 2009 viruses are antigenically distinct from previous seasonal influenza A (H1N1) human isolates, they are similar to classical swine A (H1N1) viruses and North American A (H1N1) viruses that circulated in swine in the US over the last decade, and that have occasionally infected humans during the same period (Garten et al, *Scienceexpress* /www.sciencexpress.org/ 22 May

³ The designation of the 2009 H1N1 virus as “pandemic” is derived from the World Health Organization (“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. *See* What is Phase 6?, *available at* http://www.who.int/csr/disease/swineflu/frequently_asked_questions/levels_pandemic_alert/en/index.html.

2009/Page 1/10.1126/science.1176225). The pandemic (H1N1) 2009 virus does not present a change in influenza A subtype, even though it has a unique genome composition not identified previously, based on nucleotide sequencing and phylogenetic analysis. (N Engl J. Med 2009; 361, N Engl. J. Med. 10.1056/NEJMoa09038120; N. Engl. J. Med 2009; 361. DOI: 10.1056/ NEJMoa0903810).

Id. Accordingly, although the 2009 H1N1 virus had not been previously identified, it belongs to an influenza A subtype with which FDA is very familiar.

FDA licensed four monovalent (*i.e.*, containing only the H1N1 subtype) vaccines on September 15, 2009, to MedImmune, Sanofi Pasteur, CSL Limited, and Novartis. *See* FDA Approval Memoranda (Exhibits 1-4).⁴ As set forth in its decisional memoranda, FDA considered three different regulatory options for approval:

(I) BLA strain change supplement without clinical data at the time of submission. The immunogenicity data (the measure of the vaccine's ability to induce an immune response) from ongoing clinical trials would be submitted post-licensure as a clinical efficacy supplement.

(ii) BLA or BLA strain change supplement containing limited clinical data (such as immunogenicity data following the first dose) from on-going clinical studies. The immunogenicity data following the second dose would be submitted post-licensure.

(iii) BLA with complete clinical dataset, *i.e.*, submission of a BLA when clinical studies evaluating immunogenicity and safety following two doses of the 2009 H1N1 vaccine are completed.

⁴ These documents are part of the administrative record of FDA's approval of the H1N1 vaccine licenses. FDA has not yet assembled and filed a complete administrative record in this case due to the emergency nature of plaintiffs' motion. Should any of plaintiffs' claims survive the defendants' motion to dismiss filed herewith, FDA will compile the administrative record and submit it to the Court at its earliest opportunity.

See FDA Approval Memoranda (Exhibits 1-4) at 2. FDA's most senior decisionmakers, including the Commissioner, Dr. Margaret Hamburg, and the agency's Acting Chief Scientist, Dr. Jesse Goodman, in consultation with the Office of Vaccines Research and Review, considered these regulatory options. On July 23, 2009, FDA presented the licensing strategy in option (I) above to the Vaccines and Related Biological Products Advisory Committee for discussion and received that committee's unanimous support to license the vaccine as strain change supplements without clinical data. The committee agreed with FDA that this strategy 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.

The licensed 2009 H1N1 monovalent vaccines, like the seasonal vaccines, do not contain an adjuvant, an agent that can augment the specific immune responses to antigens. *See* Influenza A (H1N1) 2009 Monovalent Vaccines Questions and Answers, *available at* <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm182335.htm>; *see also* FDA Approval Memoranda (Exhibits 1-4).⁵

B. Other Strain Change Supplements

Each year, experts from FDA, the WHO, the Centers for Disease Control and Prevention ("CDC"), and other institutions study influenza virus samples and patterns collected from around the world in an effort to identify the strains that may cause the most illness in the upcoming season. FDA works closely with CDC and vaccine manufacturers in various stages of developing seasonal

⁵ Aluminum salts are used as adjuvants in some U.S. licensed vaccines. Another adjuvant, AS04, a combination of aluminum hydroxide and monophosphoryl lipid A, is used in one U.S. licensed vaccine. *See* Common Ingredients in U.S. Licensed Vaccines, *available at* <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm187810.htm>.

vaccines, including reference virus development, reference and seed virus testing, and potency testing. FDA officials also meet with an FDA advisory committee, the Vaccines and Related Biological Products Advisory Committee, to review the strains circulating in the United States and consider the optimal strains for inclusion in the seasonal trivalent vaccines. FDA Approval Memoranda (Exhibits 1-4) at 3. FDA's approval of seasonal vaccines is described as follows:

Each new inactivated seasonal trivalent influenza vaccine (Influenza Virus Vaccine) made by currently licensed influenza vaccine manufacturers is licensed without additional clinical data specific for the new strain(s). Each new live seasonal trivalent influenza virus vaccine (Influenza Vaccine Live, Intranasal) is evaluated in approximately 300 individuals prior to approval to verify adequate attenuation. Safety and effectiveness of each new seasonal vaccine are extrapolated from data included in the approved license application as well as the post-marketing experience with preceding seasonal vaccines.

Id. at 3. FDA has a proven track record for approving seasonal flu vaccines through supplements to existing BLAs, based on the information described above.⁶

FDA has also previously licensed a monovalent vaccine like the H1N1-2009 vaccines. In 1986, FDA licensed a monovalent vaccine for a then-newly emerging antigenic variant of influenza A (H1N1) that was a significantly different influenza strain. *Id.* at 4. As with the current H1N1 strain, the 1986 vaccines were licensed based on strain change supplements without the submission of clinical data to the license. *Id.* at 5.

Notably, the current H1N1-2009 virus emerged in March 2009, after the WHO met in February 2009 to recommend appropriate strains to include in the seasonal vaccines for the

⁶ See, e.g., MMWR (July 24, 2009) (summary of studies demonstrating safety and efficacy of annual seasonal influenza vaccine in children and adults), *available at* <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm>.

northern hemisphere.⁷ In April 2009, the CDC reported that two cases of illness caused by the H1N1-2009 virus had occurred in California. On April 26, 2009, the HHS Acting Secretary determined that a public health emergency involving the H1N1-2009 virus existed.⁸ At this time, it was too late to consider including the H1N1-2009 strain in the 2009 trivalent seasonal flu vaccine. In order to make an H1N1 vaccine available in 2009, FDA had to license it as a separate, monovalent product. The WHO has recently recommended that the H1N1 strain be included in the 2010 seasonal vaccine for the southern hemisphere.⁹

C. FDA's Licensure of 2009 H1N1 Vaccines

Consistent with its well-established precedent for vaccine licensure and after consultation with its advisory committee and the agency's most senior scientists, FDA concluded that the H1N1 2009 vaccines could properly be licensed as strain change supplements based on the following:

- Safety and effectiveness extrapolated from clinical data included in the approved license application as well as the post-marketing experience with preceding seasonal

⁷ The WHO convenes technical meetings in February and September to recommend the composition of influenza vaccines for the northern and southern hemispheres, respectively. *See Recommended composition of influenza virus vaccines for use in the 2010 southern hemisphere influenza season (September 2009)*, available at http://www.who.int/csr/disease/influenza/200909_Recommendation.pdf.

⁸ *See Determination of a Public Health Emergency*, available at <http://www.flu.gov/professional/federal/index.html> (noting Acting HHS Secretary's declaration signed on April 26, 2009, and renewed by Secretary Sebelius on July 24 and October 1, 2009).

⁹ *See Recommended composition of influenza virus vaccines for use in the 2010 southern hemisphere influenza season*, available at <http://www.who.int/csr/disease/influenza/recommendations2010south/en/print.html> (recommending inclusion of "A/California/7/2009 (H1N1)-like virus").

vaccines (these data are summarized in the package inserts for each of the licensed vaccines).¹⁰

- Assurance that the H1N1 2009 virus vaccines will be manufactured using the licensed process, and will reference the nonclinical, chemistry, manufacturing, and controls (CMC) information in the already-approved BLA for the seasonal vaccine.
- For the live virus vaccine, limited clinical safety data in approximately 300 individuals.

See FDA Approval Memoranda (Exhibits 1-4) at 2-4. In addition, each applicant has initiated clinical trials to generate immunogenicity data, which will be submitted to the agency in clinical efficacy supplements. *Id.* at 3-4. The influenza A (H1N1) 2009 Monovalent vaccines are required to undergo the same rigorous testing and lot release procedures that are in place for seasonal influenza vaccines. *See* Influenza A (H1N1) 2009 Monovalent Vaccines Composition and Lot Release, *available at*

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm181956.htm>.¹¹

¹⁰ *See* Influenza A (H1N1) 2009 Monovalent, *available at* <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm>.

¹¹ FDA also had other relevant information available to it at the time of its decision, including data supporting its determination that children 9 years of age and younger should be administered 2 doses of the vaccine, and that individuals 10 years of age and older should be administered 1 dose of the vaccine. *See* FDA Approval Memoranda (Exhibits 1-4) at 4 (citing MMWR 2009; 58 (19) 521-24); *see also* Early Results from Clinical Trials of 2009 H1N1 Influenza Vaccines in Healthy Adults (Sept. 11, 2009), *available at* <http://www3.niaid.nih.gov/news/newsreleases/2009/H1N1TrialsResults.htm>; Response After One Dose of a Monovalent 2009 Influenza A (H1N1) Vaccine - Preliminary Report, *New Eng. J. Med.* (Sept. 10, 2009).

D. FDA Guidance Document

FDA was aware when it licensed the H1N1 vaccines that it had suggested in a 2007 guidance document that a full BLA, rather than a BLA supplement, might be more appropriate for licensing pandemic vaccines. *See* FDA Approval Memoranda (Exhibits 1-4) at 5 (citing Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (May 2007), *available at* <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm>). That guidance document, however, had been written in view of the agency's concern about a particularly virulent H5N1 strain for which "clinical evaluation of prospective adjuvant and unadjuvanted H5H1 subtype vaccines was considered to be an essential component of preparedness." *Id.* For the H1N1 virus, by contrast, FDA determined that it would not be necessary or appropriate to require a new, separate BLA, given the declared public health emergency, and FDA's extensive experience with the H1N1 virus in the seasonal trivalent vaccines:

In contrast to what has been observed with H5N1 influenza virus, epidemiologic data for pandemic (H1N1) 2009 virus indicate human-to-human spread and sustained community level outbreaks emphasizing the need to make a vaccine available as soon as possible. Furthermore, due to the similarities in influenza subtype between the current and previously circulating H1N1 viruses, as well as the use of the same manufacturing process for both the currently licensed seasonal trivalent influenza vaccines, and the pandemic (H1N1) 2009 vaccines, it is scientifically valid to extrapolate the safety and effectiveness data supporting licensure of the seasonal vaccines to support approval of strain change supplements for the vaccines against pandemic (H1N1) 2009 virus.

Id. at 5-6.

E. Declarations of Emergency and Emergency Use Authorizations

When the H1N1 virus emerged in the spring of 2009, the defendants took several steps to respond to the H1N1 virus, including determining on April 26, 2009, that a public health emergency existed related to the H1N1 virus pursuant to the PHSA, 42 U.S.C. § 247d. *See* Determination of a Public Health Emergency, *available at* <http://www.flu.gov/professional/federal/index.html> (noting Acting HHS Secretary's declaration signed on April 26, 2009, and renewed by Secretary Sebelius on July 24 and October 1, 2009). A declaration of a Public Health Emergency authorizes the HHS Secretary to take certain responsive actions, such as making grants, providing awards for expenses, entering into contracts, and conducting and supporting investigations into the cause, treatment, or prevention of the public health emergency. 21 U.S.C. § 247d. In addition, on October 24, 2009, President Obama issued a Declaration of National Emergency. *See* Declaration of a National Emergency with Respect to the 2009 H1N1 Influenza Pandemic, *available at* <http://www2a.cdc.gov/phlp/docs/2009H1N1%20prc%20rel.pdf>. President Obama's declaration authorizes the HHS Secretary to temporarily waive or modify the application of certain statutory and regulatory requirements, including some requirements under Medicare, Medicaid, the State Children's Health Insurance Program, and the Health Insurance Portability and Accountability Act, for health care providers in response to the national emergency caused by the 2009 H1N1 influenza pandemic. *See* 42 U.S.C. § 1320b-5.

FDA has authority to issue an Emergency Use Authorization ("EUA") to allow either the use of an unapproved medical product or an unapproved use of an approved medical product during certain types of emergencies with specified agents. *See* 21 U.S.C. § 360bbb-3. FDA has

issued EUAs for certain diagnostic and therapeutic tools to identify and respond to the 2009 H1N1 flu virus, and for the use of certain antiviral products.¹² FDA has *not*, however, issued an EUA for any 2009 H1N1 vaccines. To issue an EUA, FDA must determine that certain criteria are met, above and beyond the existence of a declaration of a public health emergency. 21 U.S.C. § 360bbb-3(c).

Separate from declarations of a public health emergency under the PHSA, the HHS Secretary may issue a Declaration for the Use of the Public Readiness and Emergency Preparedness Act (“PREP Act”). *See* 42 U.S.C. § 247d-6d(b). Such a declaration is issued to encourage the production of products that will be of use in an emergency, and may confer certain immunity from tort liability to individuals and organizations involved in the development, manufacture, distribution, administration, and use of countermeasures against pandemics, epidemics and diseases and health threats caused by chemical, biological, radiological, or nuclear agents of terrorism. *Id.* The Secretary has also issued a declaration under the PREP Act for the 2009 H1N1 virus. *See* 74 Fed. Reg. 51,153 (Oct. 5, 2009).

III. Procedural Posture

On August 24, 2009, plaintiff Gary Null, representatives of the two organizational plaintiffs,¹³ and four other individuals, filed a citizen petition with FDA seeking a temporary stay of all pending approvals for vaccines to treat the H1N1 virus. Docket No. FDA-2009-P-0418; *see* 21

¹² *See* Emergency Use Authorizations Questions and Answers, *available at* <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm153297.htm>.

¹³ In addition to plaintiff Null, the petitioners included Tedd Koren, of the Foundation for Health Choice, a plaintiff herein, and Albert N. Stubblebine III, President of the Natural Solutions Foundation, also a plaintiff in this case.

C.F.R. § 10.30. Petitioners 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.” Petition at 2. Petitioners 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. Under FDA regulations, the agency has 180 days to respond to the petition. 21 C.F.R. § 10.30(e)(2).

Barely a month and a half later, without awaiting a response from FDA, plaintiffs brought this action, seeking substantially the same relief as they sought in their citizen petition. Plaintiffs filed their complaint on October 9, 2009, requesting among other things, the “reversal” of the H1N1 vaccine approvals, and a variety of injunctive relief. *See* Complaint ¶¶ 23-24. One week later, on October 16, 2009, plaintiffs moved for a preliminary injunction and/or temporary restraining order. Plaintiffs seek an order (1) withdrawing or suspending FDA’s approval of the four vaccines; (2) requiring FDA to reveal information about the contents of the vaccines; (3) staying all approvals of any vaccines for H1N1; (4) staying FDA’s issuance of an Emergency Use Authorization for certain inactivated H1N1 vaccines; and (5) requiring FDA to make approval of the vaccines contingent upon informed consent.

Plaintiffs identify themselves as health care workers subject to a New York state regulation mandating that health care personnel receive annual influenza vaccinations as a precondition to employment. Complaint ¶¶ 4, 8-9; *see* Title 10, New York Codes, Rules and Regulations (“NYCCR”), Subpart 66-3 (“Health Care Facility Personnel - Influenza Vaccination Requirements”) (attached hereto as Exhibit 5). Plaintiffs allege that, as a result of FDA’s approval

of the H1N1 vaccines, they are at risk of being required to receive the vaccine against their will or face adverse employment consequences. *See* Complaint ¶ 11; Br. at 8.

The same day plaintiffs filed the instant motion, however, enforcement of the health care vaccination regulation was stayed by a New York state court. *See* Order to Show Cause (attached hereto as Exhibit 6). Subsequently, on October 23, 2009, the New York Commissioner of Health suspended the vaccination requirement through April 1, 2010, citing a shortage in H1N1 vaccine supplies. *See* Letter from Richard F. Daines, M.D., Commissioner of Health (October 23, 2009) (attached hereto as Exhibit 7). The suspension letter stated that “no new emergency regulations will be promulgated,” but that New York would subsequently advance permanent regulations in draft form, and publish them for public comment. *Id.* at 2. Thus, as of this date, the New York health care facility vaccination regulation is not in effect and will not resume effect until at least April 2010.¹⁴

On October 27, 2009, this Court entered a Scheduling & Show Cause Order, requiring plaintiffs to show cause why this case should not be dismissed for lack of standing. The Court noted that it was unclear “why this case should not be dismissed based on the plaintiffs’ lack of standing given that the plaintiffs would only suffer harm if either vaccinated against their will or if forced to refuse to submit to a mandatory vaccination policy upon which employment hinged, neither of which are attributable to the defendants in this matter.” Scheduling & Show Cause Order at 3.

¹⁴ In light of this action by the New York Commissioner of Health, defendants inquired of plaintiffs’ counsel whether plaintiffs intended to continue pursuing this action, and suggested that plaintiffs consider withdrawing their motion for preliminary relief. As of this date, however, plaintiffs have declined to do so.

ARGUMENT

I. Plaintiffs' Claims Should Be Dismissed for Lack of Jurisdiction

A. Plaintiffs Lack Standing to Challenge FDA's Licensure of the H1N1 Vaccines

Article III of the Constitution limits federal court jurisdiction to actual cases or controversies. *Valley Forge Christian Coll. v. Ams. United for Separation of Church and State, Inc.*, 454 U.S. 464, 471-75, 102 S. Ct. 752, 758-60 (1982). The doctrine of standing is an “essential and unchanging” component of this constitutional requirement. *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560, 112 S. Ct. 2130, 2134 (1992). Article III thus requires a party who invokes the court's authority to “‘show that he personally has suffered some actual or threatened injury as a result of the putatively illegal conduct of the defendant,’ . . . and that the injury ‘fairly can be traced to the challenged action’ and ‘is likely to be redressed by a favorable decision.’” *Valley Forge*, 454 U.S. at 472, 102 S. Ct. at 758 (quoting *Gladstone, Realtors v. Vill. of Bellwood*, 441 U.S. 91, 99, 99 S. Ct. 1601, 1608 (1979); and *Simon v. Eastern Kentucky Welfare Rights Org.*, 426 U.S. 26, 38, 41, 96 S. Ct. 1917, 1924, 1926 (1976)).

In *Lujan*, the Supreme Court articulated a three-part test for determining whether a plaintiff has satisfied the “irreducible constitutional minimum” requirements for Article III standing:

First, the plaintiff must have suffered an “injury in fact” – an invasion of a legally-protected interest which is (a) concrete and particularized and (b) “actual or imminent, not ‘conjectural’ or hypothetical.” Second, there must be a causal connection between the injury and the conduct complained of – the injury has to be “fairly . . . trace[able] to the challenged action of the defendant, and not . . . th[e] result [of] the independent action of some third party not before the court.” Third, it must be “likely,” as opposed to merely “speculative,” that the injury will be “redressed by a favorable decision.”

504 U.S. at 560-61, 112 S. Ct. at 2136 (internal citations omitted).

Because the party invoking federal jurisdiction bears the burden of demonstrating standing, *see id.* at 561, the complaint must “clearly and specifically” set forth facts sufficient to satisfy the Article III requirements. *Whitmore v. Arkansas*, 495 U.S. 149, 155, 110 S. Ct. 1717, 1723 (1990) (court may not create jurisdiction “by embellishing otherwise deficient allegations of standing”). Standing cannot be “inferred argumentatively from averments in the pleadings,” but, rather, plaintiffs “must ‘allege . . . facts essential to show jurisdiction.’” *FW/PBS, Inc. v. City of Dallas*, 493 U.S. 215, 231, 110 S. Ct. 596, 608 (1990) (citations omitted); *Warth v. Seldin*, 422 U.S. 490, 504, 95 S. Ct. 2197, 2208 (1975) (plaintiff must “allege *facts* from which it reasonably could be inferred” that elements of standing are satisfied) (emphasis added). The courts have demanded a “[f]astidious commitment” to the Article III standing requirements in order to ensure that the federal judicial power is exercised “only when the dispute is amenable to judicial resolution,” *Talenti v. Clinton*, 102 F.3d 573, 576 (D.C. Cir. 1996), and only in “the last resort.” *Allen v. Wright*, 468 U.S. 737, 752, 104 S. Ct. 3315, 3325 (1984) (quoting *Chicago & Grand Trunk Ry. Co. v. Wellman*, 143 U.S. 339, 345 (1892)).

Here, as the Court has already recognized, plaintiffs’ allegations are woefully insufficient to establish Article III standing. Plaintiffs identify themselves as “nongovernmental organizations and individual United States citizens who are members of the organizations and the general public.” Complaint ¶ 8; Br. at 7. Specifically, as noted, plaintiffs purport to be health care workers subject to a New York state regulation mandating that health care personnel receive annual influenza vaccinations as a precondition to employment. Complaint ¶ 9(A). Plaintiffs allege that, as a result of FDA’s approvals of the H1N1 vaccines, they “stand in imminent peril of risk of health or life, loss of liberty, property, livelihood or licensure, . . . [and] in imminent peril of being coerced,

mandated or required to receive the [H1N1] Vaccines against their will and without their fully informed, voluntary consent.” Complaint ¶ 11; Br. at 8.

The New York regulation on which plaintiffs rely, however, was suspended on October 23, 2009, and is no longer in effect. *See* Daines Letter (Exhibit 7). Thus, to the extent any plaintiff previously faced the prospect of mandatory vaccination, that threat has evaporated. Under these circumstances, plaintiffs cannot demonstrate that they are threatened with any “actual” or “imminent” injury, much less injury fairly traceable to FDA’s approval of the H1N1 vaccines.

Because plaintiffs have not established the requisite elements of Article III standing, their complaint should be dismissed.

1. Plaintiffs Face No Threat of Imminent Injury

In order to establish “injury in fact,” a plaintiff must allege facts sufficient to show that he or she will suffer “actual or imminent” injury as a result of the challenged conduct. *Whitmore*, 495 U.S. at 155, 110 S. Ct. at 1723. The injury must be “concrete in both a qualitative and temporal sense,” and it must be “distinct and palpable” and “actual or imminent,” not “conjectural” or “hypothetical.” *Id.* (citations omitted); *see also Lujan*, 504 U.S. at 560, 112 S. Ct. at 2136. “Allegations of possible future injury do not satisfy the requirements of [Article] III. A threatened injury must be ‘certainly impending’ to constitute injury in fact.” *Whitmore*, 495 U.S. at 158, 110 S. Ct. at 1725 (quoting *Babbitt v. Farm Workers*, 442 U.S. 289, 298, 99 S. Ct. 2301, 2309 (1979)). If the injury has not already occurred, a plaintiff must demonstrate a “credible threat” of imminent future injury, *see, e.g., Presbyterian Church (USA) v. United States*, 870 F.2d 518, 528-29 (9th Cir. 1989), and it must be real and immediate. *See Golden v. Zwickler*, 394 U.S. 103, 109, 89 S. Ct. 956, 960 (1969).

Plaintiffs' allegations of harm all stem from 10 NYCRR 66-3 which, as noted above, is no longer in effect. For example, plaintiff Gary Null states that he is a New York licensed dietician and nutritionist and that, as a result of the New York mandatory vaccination regulation, he "may be effectively barred from practicing my licensed healthcare profession unless I submit to the Vaccines." Null Certification at ¶ 10. Similarly, plaintiff Rima Laibow states that she is a New York licensed physician who, due to the regulation, "may be effectively barred from practicing medicine unless I submit to the Vaccines." Laibow Certification at ¶ 10. Likewise, plaintiffs Susanne Field, a registered nurse, Cheryl Robbins, a certified nursing assistant, Mary Kuchman, a hospital billing specialist, and Heather Walker, an occupational therapy student, all state that they are "subject" to the Health Care Facility Personnel - Influenza Vaccination Requirements, and that, accordingly, they "will be forced to receive the Vaccines or suffer serious adverse consequences to [their] protected rights and interests." Field Certification ¶ 4; Robbins Certification ¶ 4; Kuchman Certification ¶ 4; Walker Certification ¶ 4.

Even if plaintiffs faced a threat of "actual" or "imminent" injury before, any such threat was fully removed when the New York vaccination regulation was suspended by the New York State Health Commissioner on October 23, 2009. *See* Exhibit 7 (Daines Letter).¹⁵ Not only did Commissioner Daines "suspend the requirement for the health care personnel to be vaccinated against both influenza viruses for the current influenza season (through April 1, 2010)," he made clear that no new emergency regulations requiring mandatory vaccinations would be promulgated.

¹⁵ Moreover, enforcement of the regulation was stayed by a New York state court on October 16, 2009, hours *before* the plaintiffs' motion for preliminary injunction in this case was filed. *See* Order to Show Cause (Exhibit 6). Thus, even at the time they brought their motion, plaintiffs were not under any imminent threat of compelled vaccination.

Id. at 1-2. Instead, the issue would be addressed by new regulations that would be published in draft form for public comment prior to their promulgation. *Id.* Plaintiffs cannot demonstrate that they currently face any threat of “certainly impending” injury, and they fail to satisfy the requisite element of “injury in fact.” *Whitmore*, 495 U.S. at 158, 110 S. Ct. at 1725.¹⁶

2. Plaintiffs’ Alleged Injuries Are Not Fairly Traceable to FDA’s Vaccine Approvals

Equally important, any injury that plaintiffs might conceivably face in the future is in no sense “fairly traceable” to FDA’s approval of the H1N1 vaccines, the action plaintiffs seek to challenge in this case. FDA has not required plaintiffs to take H1N1 vaccine, nor has FDA threatened the plaintiffs’ employment or livelihood should they fail to do so. To the contrary, as plaintiffs’ own papers make clear, the source of plaintiffs’ alleged injury in this case is not FDA’s approval of the vaccine, but the now-suspended New York regulation requiring annual vaccination

¹⁶ Plaintiffs do not even attempt to establish standing on behalf of the organizational plaintiffs, the Natural Solutions Foundation and the Foundation for Health Choice, neither of which is described in the complaint. Although plaintiffs offer certifications from plaintiff Rima Laibow, who identifies herself as a “trustee” of the Natural Solutions Foundation, and Tedd Koren, who identifies himself as the “President” of the Foundation for Health Choice, neither states what these organizations do or how, if at all, they have been harmed by any action of the defendants.

If an organization cannot demonstrate any injury to itself, it may nevertheless be able to establish associational standing by showing that the organization’s members would have standing to sue, that the interests it seeks to protect are germane to the organization’s purpose, and that participation of individual members in the lawsuit is not necessary. *Friends of the Earth, Inc. v. Laidlaw Env’tl Servs., Inc.*, 528 U.S. 167, 181, 120 S. Ct. 693, 704 (2000); *see also Hunt v. Wash. State Apple Adver. Comm’n*, 432 U.S. 333, 343, 97 S. Ct. 2434, 2441 (1977); *Nat’l Taxpayers Union, Inc. v. United States*, 68 F.3d 1428, 1435 (D.C. Cir. 1995); *Wash. Legal Found. v. Leavitt*, 477 F. Supp. 2d 202, 207-08 (D.D.C. 2007). The allegations regarding the organizational plaintiffs here, however, do not even indicate who their members are, much less provide any facts supporting a conclusion that those members have suffered cognizable injuries, or any other requisite elements of associational standing. Thus, plaintiffs’ allegations do not establish associational standing.

of health care workers and the independent actions of plaintiffs' employers pursuant thereto. In these circumstances, as this Court has correctly observed:

[P]laintiffs would only suffer harm if either vaccinated against their will or if forced to refuse to submit to a mandatory vaccination policy upon which employment hinged, neither of which are attributable to the defendants in this matter. It is therefore unclear how the challenged actions of the defendants, the approval or licensing of the identified vaccines, are directly, or even closely, related to the actions of the State of New York or the plaintiffs' employers, the actual entities to whom the harm alleged is logically attributable.

Scheduling & Show Cause Order at 3.

Even if the New York regulation were still in effect, a party cannot maintain standing to sue the government based on injuries caused by the conduct of third parties. *See Lujan*, 504 U.S. at 560, 112 S. Ct. at 2136; *Simon*, 426 U.S. at 41-42, 96 S. Ct. at 1926; *Ctr. for Law & Educ. v. Dep't of Educ.*, 396 F.3d 1152, 1160-61 (D.C. Cir. 2005). Article III "requires that a federal court act only to redress injury that fairly can be traced to the challenged action of the defendant, and not injury that results from the independent action of some third party not before the court." *Simon*, 426 U.S. at 41-42, 96 S. Ct. at 1926. Where, as here, "the parties invoking federal jurisdiction are not 'the object of the government action or inaction' they challenge," standing is "substantially more difficult to establish." *Pub. Citizen, Inc. v. Nat'l Highway Traffic Safety Admin.*, 489 F.3d 1279, 1289 (D.C. Cir. 2007) (quoting *Lujan*, 504 U.S. at 562, 112 S. Ct. at 2137); *see also Fla. Audubon Soc'y v. Bentsen*, 94 F.3d 658, 663 (D.C. Cir. 1996) (*en banc*) (plaintiffs must demonstrate that "it is substantially probable . . . that the challenged acts of the defendant, not of some absent third party, will cause [their] particularized injury").

Here, plaintiffs' causation theory is as convoluted as it is attenuated. Plaintiffs contend that the New York vaccination regulation "provides that any future influenza vaccines recommended by

the Centers for Disease Control (‘national recommendations’), a subunit of Defendant Secretary, shall be included in the regulatory mandate, as a condition of maintaining employment.” Complaint ¶ 9(B). Thus, according to plaintiffs, FDA’s licensing of the H1N1 vaccines “is the necessary prerequisite for the recommending by the sub-unit of the Agency and for the automatic mandating of the Vaccines for the covered healthcare workers.” *Id.* In other words, plaintiffs assert standing to challenge FDA’s approval of the H1N1 vaccines because that approval is a “prerequisite” for a chain of events that could eventually lead to their receiving the vaccine, in that: (a) they are health care workers subject to the New York mandatory vaccination regulation; (b) the regulation requires annual immunization from influenza as a precondition to employment; (c) the vaccination(s) required each year are determined “in accordance with the national recommendations in effect at the time of the vaccinations(s)”; (d) the CDC makes national recommendations for vaccinations; (e) the CDC currently recommends vaccination against H1N1 influenza; (f) the CDC is a subunit of HHS, a defendant herein; (g) FDA is also a part of HHS and a defendant herein; (h) FDA approved the H1N1 vaccine licences. *See* Complaint ¶¶ 4, 9, 11 (and accompanying Certifications).

Plaintiffs’ connect-the-dots theory of causation is “attenuated at best,” and too feeble to satisfy the prerequisites of Article III standing. *Allen*, 468 U.S. at 757. The source of plaintiffs’ alleged injury – the (now-suspended) annual vaccination requirement mandated by New York law – is many levels removed from the action plaintiffs seek to enjoin – FDA’s approval of the H1N1 vaccines. FDA has not itself mandated that plaintiffs receive the H1N1 vaccine, nor has the agency (or any other HHS component, including the CDC) recommended that H1N1 vaccinations be mandatory for health care personnel or others. FDA properly approved the H1N1 vaccine

licenses, but does not control the policies of state authorities who have discretion to require that health care workers receive the vaccination as a condition of employment and whose independent choices are the true source of any alleged harm plaintiffs might suffer.¹⁷

In these circumstances, the “links in the chain of causation between the challenged Government conduct and the asserted injury are far too weak” to establish standing. *Allen*, 468 U.S. at 759, 104 S. Ct. at 3328. Plaintiffs’ theory is equivalent to suing the doctor who delivered the baby who grew-up to be the thief who stole the plaintiff’s wallet. Although causation is inherently elastic, the requirements of standing will not be satisfied “simply because a chain of events can be hypothesized in which the action challenged eventually leads to actual injury.” *Northwest Airlines, Inc. v. FAA*, 795 F.2d 195, 201 (D.C. Cir. 1986). As the Supreme Court has made clear, standing is not merely “an ingenious academic exercise in the conceivable.” *Lujan*, 504 U.S. at 566, 112 S. Ct. at 2140 (quoting *United States v. Students Challenging Regulatory Agency Procedures (SCRAP)*, 412 U.S. 669, 688, 93 S. Ct. 2405, 2416 (1973)).

Because plaintiffs have failed to establish that they have suffered an injury-in-fact, or that their asserted injuries are “fairly traceable” to the challenged FDA action, they lack standing and their complaint should be dismissed.

¹⁷ Plaintiffs’ theory of causation is thus dependent upon “the unfettered choices made by independent actors not before the courts and whose exercise of broad and legitimate discretion the courts cannot presume either to control or to predict.” *Lujan*, 504 U.S. at 562, 112 S. Ct. at 2137 (quoting *ASARCO, Inc. v. Kadish*, 490 U.S. 605, 615, 109 S. Ct. 2037, 2044 (1989)). Plaintiffs seek to overturn FDA’s actions, not because those actions themselves caused harm, but “only as a means to alter the conduct of third part[ies], not before the court, who [are] the direct source of [plaintiffs’] injury.” *Cnty. for Creative Non-Violence v. Pierce*, 814 F.2d 663, 668 (D.C. Cir. 1987) (quoting *Common Cause v. Dep’t of Energy*, 702 F.2d 245, 251 (D.C. Cir. 1983) (emphasis in original)). Such an attenuated theory of causation is insufficient to support Article III standing.

B. Plaintiffs' Claims About Adjuvanted Vaccines Are Not Ripe

To the extent that plaintiffs' claims rest on their objection to vaccines with adjuvant, those claims are not ripe. *See, e.g.*, Br. at 18 (“Of further concern is whether these Vaccines may contain ‘adjuvants’ – substances added to the Vaccines to reduce the amount of viral material used, or to force an immune system response.”). FDA has not approved any vaccines with adjuvant, nor has it issued an EUA allowing for such use. *See* FDA Approval Memoranda (Exhibits 1-4) at 1 & 3; *see also* Emergency Use Authorizations Questions and Answers, *available at* <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm153297.htm>.

Both Article III of the U.S. Constitution and the Administrative Procedure Act (“APA”), 5 U.S.C. § 704, require a final agency decision before a plaintiff seeks judicial review.¹⁸ The doctrine of ripeness is designed “to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties.” *Nat’l Park Hospitality Ass’n v. Dep’t of Interior*, 538 U.S. 803, 807-08, 123 S. Ct. 2026, 2030 (2003) (quoting *Abbott Laboratories v. Gardner*, 387 U.S. 136, 148-149, 87 S. Ct. 1507, 1515 (1967)).

“[A] claim is not ripe for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all.” *Pfizer v. Shalala*, 182 F.3d 975, 978 (D.C.

¹⁸ The ripeness doctrine, like standing, is based on Article III of the Constitution. *See Devia v. NRC*, 492 F.3d 421, 424 (D.C. Cir. 2007). The APA similarly authorizes judicial review only of “final agency action.” 5 U.S.C. § 704. The requirement of final agency action is thus both part of Article III justiciability as well as a necessary element of a cause of action under the APA.

Cir. 1999) (citing *Texas v. United States*, 523 U.S. 296, 300, 118 S. Ct. 1257, 1259 (1998)). As the D.C. Circuit candidly elaborated:

[T]he “usually unspoken element of the rationale” is this: “If we do not decide [the claim] now, we may never need to. Not only does this rationale protect the expenditure of judicial resources, but it comports with our theoretical role as the governmental branch of last resort. Article III courts should not make decisions unless they have to.” *Nat’l Treasury Emples. Union*, 101 F.3d at 1431 (citation omitted).

Devia, 492 F.3d at 424-25.

Ripeness turns upon two primary considerations: (1) “the fitness of the issues for judicial decision” and (2) “the hardship to the parties of withholding court consideration.” *Abbott Laboratories*, 387 U.S. at 149, 87 S. Ct. at 1515; accord *Toilet Goods Ass’n v. Gardner*, 387 U.S. 158, 162, 87 S. Ct. 1520, 1523 (1967); see also *Nevada v. DOE*, 457 F.3d 78, 84 (D.C. Cir. 2006) (citing *Ohio Forestry Ass’n, Inc. v. Sierra Club*, 523 U.S. 726, 733, 118 S. Ct. 1665, 1670 (1998)). The fitness prong, in turn, depends upon (a) whether the claims raise purely legal questions, and (b) whether the challenge involves final agency action. *Toilet Goods Ass’n*, 387 U.S. at 163-64, 87 S. Ct. at 1523-24; *Abbott Laboratories*, 387 U.S. at 149, 87 S. Ct. at 1515-16. Here, plaintiffs’ claims regarding adjuvanted vaccines appear to be based on their misunderstanding of the facts, or their fears of what FDA may do in the future, *i.e.*, issue an EUA for adjuvanted vaccines. Plaintiffs’ fears are not fit for review, and plaintiffs will suffer no hardship if this Court declines to review their claims based on their speculation as to what FDA may do in the future, particularly after New York’s suspension of the mandatory vaccination regulation. Plaintiffs’ claims regarding adjuvanted vaccines are thus manifestly unripe.

II. Plaintiffs Are Not Entitled to Preliminary Injunctive Relief

Even if this Court were to consider plaintiffs' motion for preliminary injunction, plaintiffs have failed to establish any of the requirements for such relief. Preliminary injunctive relief is an "extraordinary and drastic remedy" that should be sparingly exercised. *Mazurek v. Armstrong*, 520 U.S. 968, 972, 117 S. Ct. 1865, 1867 (1997); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 215 (D.D.C. 1996). To obtain a temporary restraining order or a preliminary injunction, a party must demonstrate that: (1) it has a substantial likelihood of success on the merits; (2) it will suffer irreparable injury in the absence of preliminary relief; (3) other interested parties will not be substantially injured if the requested relief is granted; and (4) granting such relief would serve the public interest. *See Katz v. Georgetown Univ.*, 246 F.3d 685, 687-88 (D.C. Cir. 2001); *see also Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 160 (D.D.C. 2006).

The likelihood of success requirement is the most important of these factors. *Id.* Indeed, "[w]ithout any probability of prevailing on the merits, the Plaintiffs' purported injuries, no matter how compelling, do not justify preliminary injunctive relief." *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 38 F. Supp. 2d 114, 140 (D.D.C. 1999). As the Supreme Court recently made clear, "a party seeking a preliminary injunction must demonstrate . . . 'a likelihood of success on the merits,'" not merely the existence of "questions 'so serious, substantial, difficult and doubtful, as to make them fair ground for litigation[.]'" *Munaf v. Geren*, 128 S. Ct. 2207, 2219 (2008) (citations omitted).

Nor is a mere "possibility" of irreparable harm sufficient to justify a preliminary injunction:

Our frequently reiterated standard requires plaintiffs seeking preliminary relief to demonstrate that irreparable injury is *likely* in the absence of an injunction. . . . Issuing a preliminary injunction based only on a possibility of irreparable harm is

inconsistent with our characterization of injunctive relief as an extraordinary remedy that may only be awarded upon a clear showing that the plaintiff is entitled to such relief.

Winter v. NRDC, Inc., 129 S. Ct. 365, 375-76 (2008) (citations omitted, emphasis in original).

Moreover, the preliminary relief that plaintiffs seek in this case is not to preserve the status quo, but to overturn FDA's approval of the H1N1 vaccines, which are being dispensed around the country at this very moment. A court's power to issue such a mandatory injunction "should be sparingly exercised." *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 36 (D.D.C. 2000).

A. Plaintiffs Have No Likelihood of Success on the Merits

As demonstrated above, plaintiffs lack standing to maintain this action and their claims regarding adjuvanted vaccines are unripe. Because plaintiffs' complaint is thus subject to dismissal for lack of subject matter jurisdiction, they have *no* likelihood of success on the merits. Even if the Court were to reach the merits of plaintiffs' claims, however, they would be highly unlikely to prevail.

1. FDA's Scientific and Regulatory Determinations, Particularly as to the Approval of Drugs and Vaccines, Are Due Substantial Deference

FDA's administrative decisions are subject to review by this Court under the APA, and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416, 91 S. Ct. 814, 824 (1971). It starts with "a presumption in favor of the validity of the administrative action," *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996), and requires the Court to uphold the action so long as it is "rational, based on consideration of the relevant factors, and within the scope

of the authority delegated to the agency by statute.” *Motor Vehicle Mfrs. Ass’n of the United States, Inc., v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42, 103 S. Ct. 2856, 2866 (1983); *see also Overton Park*, 401 U.S. at 416, 91 S. Ct. at 824; *AT&T Corp. v. FCC*, 349 F.3d 692, 698 (D.C. Cir. 2003).

When, as here, an agency’s decision is based on evaluation of scientific information within the agency’s areas of technical expertise – here, scientific evaluations of vaccine safety and effectiveness, and protecting the public from dangerous epidemics – the degree of deference is even greater. *Sw. Pa. Growth Alliance v. Browner*, 121 F.3d 106, 117 (3d Cir. 1997); *see also Int’l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) (“The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise.”). Courts “review scientific judgments of the agency ‘not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.’” *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)). Recognizing that “FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug,” courts routinely “defer to its reasonable findings.” *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996); *see also Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA’s “judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA’s expertise and merit deference from us”); *Tri-Bio Laboratories, Inc. v. United States*, 836 F.2d 135, 142 (3d Cir. 1987) (“in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful

consideration by this court”); *Nat’l Ass’n of Metal Finishers v. EPA*, 719 F.2d 624, 657 (3d Cir. 1983) (“the choice of scientific data and statistical methodology to be used is best left to the sound discretion of the [agency]”), *rev’d on other grounds*, 470 U.S. 116, 105 S. Ct. 1102 (1985).

This principle of deference is well illustrated by the D.C. Circuit’s recent decision in *Rempfer v. Sharfstein*, No. 08-5117, 2009 U.S. App. LEXIS 21344 (D.C. Cir. Sept. 29, 2009), which involved a challenge to FDA’s determination that the anthrax vaccine was effective, regardless of the route of exposure (inhalational through the lungs, or cutaneous through the skin). The court rejected the plaintiffs’ assertion that the route of exposure was scientifically relevant, noting that “FDA’s contrary determination is a scientific judgment within its ‘area of expertise,’ the kind of judgment to which this court gives a ‘high level of deference.’” *Id.* at *17.

2. FDA Followed the Appropriate Statutory and Regulatory Framework in Approving the Vaccines

FDA approved the H1N1 vaccines as strain change supplements, an approach that is wholly appropriate under the applicable statutes and FDA’s regulation at 21 C.F.R. § 601.12. As described above, FDA has consistently applied this same approach in approving the trivalent seasonal flu vaccines and at least one other monovalent vaccine. Plaintiffs raise a host of objections to FDA’s approval decision, none of which have any merit.

Plaintiffs first contend that the manufacturers should have submitted full new applications for their vaccines, pursuant to 21 C.F.R. § 601.2(a). *Br.* at 16. They argue that the agency’s decision to treat the vaccine as a change-of-strain rather than requiring submission of a full application is contrary to the “Agency’s own position” that the 2009 H1N1 virus is “novel,” and is arbitrary and capricious. *Id.* at 18.

Although the 2009 H1N1 strain is “antigenically distinct” from previous H1N1 strains, it is “similar to classical swine A (H1N1) viruses and North American A(H1N1) viruses that circulated in swine in the US over the last decade, and that have occasionally infected humans during the same period.” FDA Approval Memoranda (Exhibits 1-4) at 2. “The pandemic (H1N1) 2009 virus does not present a change in influenza A subtype, even though it has a unique genome composition not identified previously, based on nucleotide sequencing and phylogenetic analysis.” *Id.* Thus, although the specific 2009 H1N1 virus strain had not been previously identified, it belongs to an influenza A subtype with which FDA is very familiar.¹⁹

Because FDA is familiar with the H1N1 subtype in seasonal vaccines, FDA reasonably opted to approve the H1N1-2009 vaccines using the same regulatory approach: a strain change supplement. The information provided in the supplements provided an ample basis for approving the H1N1-2009 vaccine, which has only one virus strain (H1N1), as opposed to the three strains in the seasonal vaccines. *See* FDA Approval Memoranda (Exhibits 1-4).

Plaintiffs next argue that FDA was “statutorily required” to reject the vaccines’ approval because it is “more likely than not” that the vaccines cause adverse effects of “pandemic magnitude,” and that FDA and/or the CDC knew of this data and intentionally exposed the public to these “serious risks of harm,” while “attempting to hide/alter the data that showed the harm.” Br. at 17. Not surprisingly, plaintiffs cite nothing in support of these wildly unfounded accusations, which are simply not tethered to reality. FDA carefully considered the appropriate

¹⁹ Plaintiffs take issue with FDA’s assertion that it has “decades of experience with H1N1,” stating that the last “swine flu” episode was in 1976. Br. at 12. In fact, the H1N1 subtype has been present in most of the licensed seasonal, trivalent vaccines since 1978, as explained in FDA’s regulatory approval memoranda. *See, e.g.,* Exhibit 1, at 4.

regulatory approach and approved the vaccines with sufficient and appropriate information. *See* FDA Approval Memoranda, Exhibits 1-4. Plaintiffs were free to – and did – petition the agency to present any information they believed was relevant to FDA’s approval. *See* Docket No. FDA-2009-P-0418, *available at* www.regulations.gov. The information they submitted is part of the administrative record in this case and is publicly available. FDA considered all relevant information and came to a different conclusion than plaintiffs. In contrast to plaintiffs’ baseless allegations, FDA’s decision, based upon its review of all available data and its expert scientific judgment, merits “considerable deference.” *See, e.g., Troy*, 120 F.3d at 283.

Plaintiffs also argue that “[u]ntil the government is able to specify what drugs it has approved and how it can authorize the release of 2009-H1N1-A virus into the environment, to be used on the public in a ‘live virus’ vaccine, no license should be permitted to be effective by this Court.” Br. at 21-22. FDA has already provided extensive information about the one live and three inactivated vaccines that it approved, including all of the ingredients in the vaccines.²⁰ As set forth in FDA’s regulatory approval memorandum for the live virus vaccine, FDA required MedImmune to conduct pre-licensure safety testing for its vaccine, consistent with the requirements for live seasonal vaccine. In approving MedImmune’s live vaccine, FDA relied on this clinical safety data, as well as the extrapolation of safety and effectiveness from clinical data included in the approved license application and the post-marketing experience with preceding seasonal vaccines (which are summarized in MedImmune’s package insert); and the assurance that the H1N1 2009 virus vaccine will be manufactured using the licensed process, and will reference

²⁰ *See* Influenza A (H1N1) 2009 Monovalent, *available at* <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm>.

the nonclinical, chemistry, manufacturing, and controls (“CMC”) information in the already-approved BLA for the seasonal vaccine. *See* Exhibit 1 at 2-4.

Similarly, in approving the inactivated vaccines produced by CSL, Sanofi Pasteur, and Novartis, FDA relied on the extrapolation of safety and effectiveness from clinical data included in the approved license application and the post-marketing experience with preceding seasonal vaccines (which are summarized in the package inserts); and the assurance that the H1N1 2009 virus vaccine will be manufactured using the licensed process, and will reference the nonclinical, CMC information in the already-approved BLAs for the seasonal vaccines. *See* FDA Approval Memoranda (Exhibits 2-4) at 2-4. FDA’s determination that each of the vaccines satisfies the regulatory approval requirements is based on decades of experience with seasonal vaccines and with H1N1 in particular, and is not arbitrary and capricious.

Finally, plaintiffs contend that FDA “capriciously and arbitrarily ignored 21 U.S.C. 393(b)(2)” and the statutory provisions related to new drug approvals by approving the vaccines without adequate or any safety testing.” Br. at 23. The general mission statement embodied in 21 U.S.C. § 393(b)(2) states that “The Administration shall . . . with respect to [regulated] products, protect the public health by ensuring that . . . human and veterinary drugs are safe and effective.” This statute “underscores FDA’s authority to determine how best to ensure the safety and effectiveness of [products regulated by FDA].” *See Jerome Stevens Pharms. v. FDA*, 319 F. Supp. 2d 45, 56-57 (D.D.C. 2004) (citing *Safe Energy Coalition v. U.S. Nuclear Regulatory Comm’n.*, 866 F.2d 1473, 1478 (D.C. Cir. 1989)), *rev’d on other grounds by Jerome Stevens Pharms. v. FDA*, 402 F.3d 1249 (D.C. Cir. 2005). That statute does not confer any substantive right upon plaintiffs to challenge an agency action apart from the APA. *See id.*

3. FDA Licensed Only Unadjuvanted Vaccines

Plaintiffs baldly assert that the approved H1N1 vaccines may contain adjuvants that are unsafe. Br. at 18-19. Again, plaintiffs are wrong. FDA licensed only unadjuvanted vaccines. *See* FDA Approval Memoranda (Exhibits 1-4) at 1. As noted above, plaintiffs cannot sustain a challenge to actions that FDA has not taken based upon speculation about what the agency may or may not do in the future. *See Texas*, 523 U.S. at 300, 118 S. Ct. at 1259 (“A claim is not ripe for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all.”) (internal quotation marks omitted).

Plaintiffs’ claims regarding the alleged inclusion of “squalene” fail for similar reasons. Plaintiffs contend that FDA’s “tacit” approval of squalene violates a 2005 decision by Judge Sullivan enjoining the military from using the anthrax vaccine, which plaintiffs asserted contained squalene as an unapproved drug substance. Br. at 20. The licensed H1N1 vaccines, however, do not contain any adjuvant, nor do they contain squalene, as is evident from the package inserts, which fully disclose the ingredients for each of the licensed vaccines and are posted on FDA’s website.²¹ *See* Influenza A (H1N1) 2009 Monovalent, *available at* <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm>. Because plaintiffs’ claims about squalene and adjuvants are based on mistaken factual premises, they should be rejected.

²¹ Plaintiffs also incorrectly assert that the government is bound in this matter by the factual and legal determinations in Judge Sullivan’s 2005 decision in the anthrax vaccine litigation. Although the government may have been bound by that order in the anthrax vaccine litigation, it has no bearing on this unrelated proceeding involving different parties and an entirely different set of facts.

4. FDA Has Not Issued an EUA for the H1N1 Vaccines

Plaintiffs opine that the H1N1 flu virus is “not in a pandemic state nor is it particularly dangerous,” and that “no reasonable finder of fact could conclude that there is any ‘emergency’ for which an EUA can be lawfully issued.” Br. at 24. Plaintiffs also believe, mistakenly, that the Secretary’s PREP Act declaration “permit[s] FDA to issue an ‘Emergency Use Authorization’ (EUA) order” for administration of unapproved vaccines. *Id.* at 9. The HHS Secretary’s PREP Act declaration is not a predicate action for an EUA. *See* 21 U.S.C. § 360bbb-3(b)(1)(C) (listing three separate types of predicate emergency declarations, including a declaration under 42 U.S.C. § 247d (section 319 of the Public Health Service Act), which is distinct from a PREP Act declaration under 42 U.S.C. § 247d-6d(b)). Although the Secretary’s declaration of a public health emergency under section 319 of the Public Health Service Act (not the PREP Act declaration) could theoretically be used as a basis for a future EUA for the H1N1 vaccines, FDA could not do so without, among other things, first finding that several criteria have been satisfied in addition to the Secretary’s emergency declaration under the PHSA. *See* 21 U.S.C. § 360bbb-3(c). Thus, to the extent plaintiffs seek to assert a claim based upon the speculative possibility that FDA could issue an EUA in the future for H1N1 vaccines, any such claim is manifestly unripe. *See Texas*, 523 U.S. at 300.

5. Plaintiffs Cannot Enforce 42 U.S.C. § 300aa-27(a) or 21 U.S.C. § 351(a) Against the Defendants

Plaintiffs fare no better in arguing that FDA’s licensure of the H1N1 vaccines violates 42 U.S.C. § 300aa-27(a), a provision of the National Childhood Vaccine Injury Compensation Act of 1986 (“Childhood Vaccine Act”). Br. at 27-28. As its name indicates, the Childhood Vaccine Act

does not pertain to the standards of approval for vaccines, but to a no-fault compensation system for individuals who have been injured by vaccines routinely administered to children. 42 U.S.C. §§ 300aa-1 *et seq.* The section cited by plaintiffs, § 300aa-27(a), endows the Secretary of HHS with a broad policy mandate to administer the Childhood Vaccine Act and other pertinent laws. Specifically, under § 300aa-27(a), the Secretary of HHS is required to “promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those on the market [on December 22, 1987],” and “make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.” 42 U.S.C. § 300aa-27(a)(1), (2).

This broad mandate imposes no enforceable requirements upon the Secretary as to how improvements are to be accomplished through the use of the Secretary’s enumerated authorities, nor does it otherwise direct the Secretary to take any specific actions. Instead, § 300aa-27(a) grants unfettered discretion to the Secretary to determine the appropriate manner in which to accomplish the statute’s goals. The Secretary’s actions under this provision are thus “committed to agency discretion by law,” and not reviewable. *See Heckler v. Chaney*, 470 U.S. 821, 830-31, 105 S. Ct. 1649, 1656 (1985); 5 U.S.C. § 701(a)(2).

This Court should decline plaintiffs’ invitation to entangle itself in a policy debate regarding how best to effectuate the statute’s goal of promoting safer childhood vaccines. FDA has already licensed the H1N1 vaccines as safe, pure, and potent. Although plaintiffs may attempt to assert a claim under the APA challenging the agency’s actions, they cannot assert that FDA’s approval fails

to satisfy § 300aa-27(a) merely because it is possible that the Secretary could have taken additional steps more to plaintiffs' liking, when FDA has determined that the vaccines are safe and satisfy the requirements for approval.

Plaintiffs' reliance on *Berkovitz v. United States*, 486 U.S. 531, 108 S. Ct. 1954 (1988), to show that defendants have a "clear, nondiscretionary mandate" under § 300aa-27(a)(2) to assure safer vaccines, is misplaced. Br. at 27. In *Berkovitz*, the plaintiffs sought compensation under the Federal Tort Claims Act ("FTCA"), arguing that the polio vaccine did not meet the regulatory licensing requirements, and that the particular lot that had caused their alleged injuries should not have been released. Plaintiffs did not claim that the Secretary had violated a discretionary provision in § 300aa-27(a) to promote better childhood vaccines. Thus, the Court's conclusion that the approval itself was nondiscretionary for purposes of the FTCA does not suggest that plaintiffs have a claim against the Secretary under § 300aa-27(a), which imposes no specific requirements upon the Secretary to create heightened standards for approval.

Elsewhere in their brief (but not in their complaint), Plaintiffs assert that "injunctive relief" and "damages" are warranted under 42 U.S.C. § 300aa-31. Br. at 17 (citing § 300aa-31 and 28 U.S.C. § 1331). Section 300aa-31 provides that certain individuals may bring an action against the Secretary for violating duties under the Childhood Vaccine Act as follows:

Except as provided in subsection (b), any person may commence in a district court of the United States a civil action on such person's own behalf against the Secretary where there is alleged a failure of the Secretary to perform any act or duty under this part [42 U.S.C. §§ 300aa-10 *et seq.*].

42 U.S.C. § 300aa-31(a). This provision does not authorize "injunctive relief" or "damages;" nor does it confer standing on these plaintiffs based on their allegation that the Secretary violated

§ 300aa-27(a). Although other sections of §§ 300aa-10 *et seq* might impose enforceable duties upon the Secretary, § 300aa-27(a) is not one that does. Plaintiffs have no claim under § 300aa-31(a) to assert the violation of a general duty to make childhood vaccines safer. In addition, § 300aa-31(b) requires 60 days' written notice before commencing an action, which plaintiffs did not provide. Thus, to the extent plaintiffs seek to invoke § 300aa-31(a), they have neither complied with its requirements, nor pled any such cause of action in their complaint. Accordingly, plaintiffs' reliance on 42 U.S.C. § 300aa-31(a) is unavailing.

Plaintiffs' claim that the H1N1 vaccines are adulterated because they may contain "the allegedly dangerous live pandemic flu virus 2009-H1N1-A, Thimerosal (mercury), and the unapproved adjuvant, MF59 (which is believed to contain squalene)" is equally untenable. Br. at 25. Plaintiffs have no private right of action to enforce the FDCA prohibition against adulteration in 21 U.S.C. § 351(a). *See* 21 U.S.C. § 337(a); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4, 121 S. Ct. 1012, 1018 n.4 (2001); *Merrell Dow Pharms., Inc. v. Thompson*, 478 U.S. 804, 810-12, 106 S. Ct. 3229, 3234 (1986).

In any event, FDA's approval of the H1N1 vaccine licenses reflects the agency's well-founded conclusion that all of the approved vaccines – including MedImmune's live virus vaccine, and some that contain small amounts of thimerosal as a preservative – are safe, pure, and potent and thus meet the statutory standard for approval. In fact, live viruses and thimerosal have long been used in seasonal vaccines – products for which FDA has a proven track record of safety.²² In light of FDA's expert scientific judgment as to the safety of the H1N1 vaccines, plaintiffs' claims

²² By regulation, FDA requires that multi-use vials contain a preservative (such as thimerosal). 21 C.F.R. § 610.15(a).

of adulteration are of no moment and do not advance their challenge to FDA's approval of the vaccine licenses.

6. Plaintiffs' Constitutional Arguments Are Frivolous

Plaintiffs argue that “[t]he violation of the proper approval and licensing process, and the evident lack of transparency, rises to [*sic*] level of substantive due process violation,” citing the “rights to liberty and property protected by the 14th Amendment,” and the “4th and 5th Amendment rights to privacy and the control of their own health care choices.” Br. at 28. Plaintiffs also assert that the FDA and/or the CDC “violated the 14th Amendment’s ‘Constitutional Safety Guarantees.’” *Id.* at 17. These argument merit little attention. Indeed, aside from a cursory assertion that the New York mandatory vaccination regulation violates the 14th Amendment, plaintiffs’ complaint is devoid of even a citation to any provision of the Constitution, much less a properly pled constitutional claim.

In any event, the 14th Amendment applies to the actions of a state, not the federal government. *United Transp. Serv. Employees ex rel. Washington v. Nat’l Mediation Bd.*, 179 F.2d 446, 453 (D.C. Cir. 1949) (“The guarantees of the Fourteenth Amendment . . . apply to state action only; the limitations of the Fifth Amendment, to action of the Federal Government.”). Any asserted 14th Amendment claim against the defendants must therefore fail.

Plaintiffs fare no better under the Fifth Amendment. The substantive due-process rights plaintiffs purport to invoke attach only when a “fundamental” interest is at stake. *See Abigail Alliance v. Eschenbach*, 495 F.3d 695, 702 (D.C. Cir. 2007). Here, plaintiffs have not asserted any fundamental right that it is (1) “objectively, ‘deeply rooted in this Nation’s history and tradition,’” *Washington v. Glucksberg*, 521 U.S. 702, 721, 117 S. Ct. 2258, 2268 (1997); and (2)

“‘implicit in the concept of ordered liberty,’ such that ‘neither liberty nor justice would exist if [it] were sacrificed.’” *Id.* To the contrary, plaintiffs’ asserted liberty interest appears to be the right not to receive the H1N1 vaccines, which is irrelevant now that the New York regulation that would have subjected them to mandatory vaccination has been suspended. To the extent that plaintiffs purport to have a liberty interest in having FDA follow the “proper approving and licensing process,” Br. at 28, plaintiffs do not and cannot assert that such an interest is “deeply rooted” or that “liberty” and “justice” would be sacrificed by requiring them to raise their challenge under the APA instead of the Constitution.

Plaintiffs’ conclusory references to “their 4th and 5th Amendment rights to privacy and the control of their own health care choices” are equally unavailing. Indeed, the Fourth Amendment’s guarantee of “[t]he right of the people to be secure in their persons, houses, papers, and effects, against unreasonable searches and seizures” has no applicability to this case whatsoever. Plaintiffs’ citation to their “7th Amendment right to a jury trial in the event they suffer damages” from the H1N1 vaccine is likewise inapposite. Plaintiffs have not taken the H1N1 vaccine or been ordered to do so, let alone been injured as a result thereof. Any claim regarding the right to a jury trial is patently unripe in the absence of any injury or claim for compensation. Thus, plaintiffs’ reliance on the Seventh Amendment, like the rest of its constitutional contentions, is misplaced.

B. Plaintiffs Have Not Demonstrated Irreparable Harm and the Balance of Hardships Weighs Strongly Against Injunctive Relief

Not only have plaintiffs failed to make the requisite showing of likely success on the merits of their claims, they have failed to demonstrate that they will suffer irreparable harm absent injunctive relief or that the balance of harms weighs in their favor.

1. Plaintiffs Will Not Suffer Irreparable Harm Absent Preliminary Relief

“The *sine qua non* of granting any preliminary injunctive relief is a clear and convincing showing of irreparable injury to the plaintiff.” *Experience Works, Inc. v. Chao*, 267 F. Supp. 2d 93, 96 (D.D.C. 2003). Because plaintiffs’ likelihood of success on the merits is exceedingly slim, they “would have to make a very substantial showing of severe irreparable injury” to prevail on their motion. *Nat’l Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37, 41 (D.D.C. 1999); *see TD Int’l, LLC v. Fleischmann*, Civ. No. 09-867, 2009 WL 2390402 at *1 (D.D.C. Aug. 4, 2009) (“If the plaintiff makes a particularly weak showing on one factor . . . the other factors may not be enough to compensate.”) (quoting *Dodd v. Fleming*, 223 F. Supp. 2d 15, 20 (D.D.C. 2002)).

Irreparable injury is a very high standard. *See RCM Technologies, Inc. v. Beacon Hill Staffing Group*, 502 F. Supp. 2d 70, 74 (D.D.C. 2007); *Varicon Int’l v. OPM*, 934 F. Supp. 440, 447 (D.D.C. 1996). “The mere possibility of irreparable harm is not enough.” *TD Int’l*, 2009 WL 2390402 at *1. The injury alleged must be “both certain and great,” and it must be “actual and not theoretical.” *Wis. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985). As the D.C. Circuit has explained: “Injunctive relief will not be granted against something merely feared as liable to occur at some indefinite time, . . . the party seeking injunctive relief must show that [t]he injury complained of [is] of such imminence that there is a ‘clear and present’ need for equitable relief to prevent irreparable harm.” *Id.* (citations and internal quotation marks omitted).

Here, as noted above, the New York regulation mandating annual vaccinations for health care workers has been suspended and will not be reinstated this year. Plaintiffs thus face no threat of imminent harm. They can choose to be vaccinated or not, but they will not be required by law to receive H1N1 vaccinations as a condition of their employment. In these circumstances,

plaintiffs will suffer no irreparable harm in the absence of preliminary injunctive relief.

2. The Entry of Injunctive Relief Would Substantially Harm Others and Would be Contrary to the Public Interest

By contrast, entry of the injunctive relief plaintiffs seek would cause substantial harm to others who want to be vaccinated, and would be manifestly contrary to the public interest. Suspending FDA's approval of the vaccines – even temporarily – would deny millions of Americans the ability to protect themselves and their families from a dangerous strain of influenza, literally placing lives at risk and jeopardizing the public health. It is telling that plaintiffs' brief does not even discuss the balance of harms. Despite the fact that plaintiffs are no longer under any mandate to receive the vaccine, they nevertheless seek to deprive others of the option to choose to receive this safe and effective vaccine, needlessly exposing them to the risk of serious illness and impeding the efforts of public health officials to battle a worldwide influenza pandemic. Because plaintiffs will suffer no harm in the absence of preliminary injunctive relief, while the entry of such relief would cause untold harm to others and to the public health, the balance of harms weighs decisively against entry of a preliminary injunction.

CONCLUSION

For the foregoing reasons, plaintiffs' complaint should be dismissed for lack of subject matter jurisdiction and failure to state a claim upon which relief can be granted, and their motion for preliminary injunction should be denied.

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October 28, 2009

EXHIBIT 1



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: September 15, 2009

To: File STN 125020/1215

From: Norman W. Baylor, PhD, *Norman W. Baylor*
Director, Office of Vaccines Research and Review (OVR)

Subject: Licensure of unadjuvanted, monovalent (H1N1) influenza virus vaccines for the 2009 H1N1 pandemic as a strain change supplement

Product: Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal

Manufacturer: MedImmune LLC

I. INTRODUCTION

This memorandum summarizes the regulatory basis for FDA's approval of a supplement under Section 351 of the Public Health Service Act to MedImmune's biologics license application (BLA) for Influenza Vaccine Live, Intranasal to include unadjuvanted, Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal for the 2009 pandemic.

II. REGULATORY FRAMEWORK FOR APPROVAL

II a. Regulatory Options:

The extent of global disease due to pandemic (H1N1) 2009 virus emphasizes the need for development and timely deployment of vaccine. FDA has considered applicable regulatory options to facilitate the licensure of unadjuvanted, monovalent vaccines against pandemic (H1N1) 2009 virus. These options only pertain to unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines manufactured using the same processes as used for currently U.S. licensed trivalent seasonal vaccines and formulated to contain the same quantity of antigen as a single strain of the seasonal vaccine:

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- (i) BLA strain change supplement without clinical data at the time of submission. The immunogenicity data from ongoing clinical trials would be submitted post-licensure as a clinical efficacy supplement.
- (ii) BLA or BLA strain change supplement containing limited clinical data such as post-dose one immunogenicity data from on-going clinical studies. The post-dose 2 immunogenicity data would be submitted post-licensure.
- (iii) BLA with complete clinical dataset, i.e., submission of a BLA when clinical studies evaluating immunogenicity and safety following two doses of the 2009 H1N1 vaccine are completed.

OVRP discussed these options with FDA senior management including Drs. Margaret Hamburg, Jesse Goodman, Mary Lou Valdez and Murray Lumpkin on June 5, 2009. On July 10, 2009, representatives from FDA briefed staff from the Department of Health and Human Services (DHHS) and other Agencies within DHHS on these licensure issues during a meeting attended by, among others, HHS Chief of Staff Laura Petrou, ASPR Dr. Nicole Lurie, Dr. Bruce Gellin (NVPO) and Dr. Anthony Fauci (NIAID). FDA noted that in the case of an urgent public health need for a pandemic (H1N1) 2009 influenza vaccine, option (i) above, i.e., submission of a BLA strain change supplement without clinical data at the time of submission, provides the most expeditious regulatory pathway to licensure among the legally permissible options. Furthermore, this option is consistent with previous FDA regulatory decisions concerning influenza vaccines.

On July 23, 2009, FDA presented this licensure strategy to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) for discussion and received unanimous support from the VRBPAC members for licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 influenza vaccines as strain change supplements.

II b. Characteristics of Pandemic (H1N1) 2009 Virus:

The pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as those present in currently licensed seasonal trivalent influenza vaccines. Influenza A virus H1N1 subtypes have circulated globally from at least the mid-1930s until 1957, reappeared in 1977 and have since caused influenza disease in the United States (*MMWR*, 1986; 35 (32); 517-21; *MMWR*, 2005; 54(RR-8):1-40).

Although pandemic (H1N1) 2009 viruses are antigenically distinct from previous seasonal influenza A (H1N1) human isolates, they are similar to classical swine A (H1N1) viruses and North American A (H1N1) viruses that circulated in swine in the US over the last decade, and that have occasionally infected humans during the same period (*Garten et al, Scienceexpress* /www.scienceexpress.org/ 22 May 2009/Page 1/10.1126/science.1176225). The pandemic (H1N1) 2009 virus does not present a change in influenza A subtype, even though it has a unique genome composition not identified previously, based on nucleotide sequencing and phylogenetic analysis. (*N Engl J. Med* 2009; 361, *N Engl. J. Med.* 10.1056/NEJMoa09038120; *N. Engl. J. Med* 2009; 361. DOI: 10.1056/NEJMoa0903810).

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II c. Seasonal Influenza Vaccine Strain Change Supplements:

Gradual antigenic change in the influenza virus hemagglutinin (HA) and neuraminidase (NA) antigens requires annual assessment of influenza vaccine strains as well as annual administration of the trivalent seasonal influenza vaccine. Therefore, each year FDA and the VRBPAC consider the optimal strains for inclusion in the seasonal trivalent vaccines. Following strain selection manufacturers submit strain change supplements to their license applications. Each new inactivated seasonal vaccine (Influenza Virus Vaccine) made by currently licensed influenza vaccine manufacturers is licensed without additional clinical data specific for the new strain(s). Each new live influenza virus vaccine (Influenza Vaccine Live, Intranasal) is evaluated in approximately 300 individuals prior to approval to verify adequate attenuation. Safety and effectiveness of each new seasonal vaccine are extrapolated from data included in the approved license application as well as the post-marketing experience with preceding seasonal vaccines. Approved dosing regimens for seasonal trivalent vaccine for children and adults usually remain unchanged for strain change supplements and are based on clinical studies performed in the 1970s that demonstrated that children and adults unexposed to influenza either through natural infection or vaccination required two doses of inactivated vaccine to achieve acceptable antibody levels while persons with pre-existing immunity required a single dose (*Plotkin and Orenstein 4th edition, p. 350*). Moreover, among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (*Gross et al. J Clin Microbiol 1987;25:1763-5. Feery et al. Med J Aust 1976;1:186, 188-9, and Levine et al. CMAJ 1987;137:722-6*). This suggests that these individuals are immunologically primed to respond adequately to a single dose of vaccine formulated with an influenza subtype that is closely related to previous subtypes..

II d. Unadjuvanted, Monovalent, Pandemic (H1N1) 2009 Virus Vaccines Strain Change Supplements:

Manufacturers of licensed seasonal influenza vaccines file a manufacturing strain change supplement to their existing BLA for the trivalent seasonal vaccine. The unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine will be manufactured using the licensed process and will be considered a strain change. Consistent with the data required for the seasonal vaccine strain change, clinical safety and immunogenicity data at the time of licensure will not be required for an inactivated unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine. For unadjuvanted, monovalent pandemic (H1N1) 2009 live virus vaccine, as is the case with the seasonal live attenuated influenza vaccine, limited clinical safety data will be provided prior to licensure. Safety and effectiveness of each monovalent vaccine is extrapolated from data included in the approved seasonal license application as well as the post-marketing experience with seasonal vaccines. Each strain change supplement for pandemic (H1N1) 2009 vaccine will reference the nonclinical, chemistry, manufacturing, and controls (CMC) information and clinical data in the original approved BLA for trivalent influenza vaccine. MedImmune has initiated clinical studies with monovalent Influenza A (H1N1) 2009 Vaccine to determine the, number of doses. These data will be submitted to each license application as clinical efficacy supplements after approval of the strain change supplements.

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Although pandemic (H1N1) 2009 virus belongs to the same influenza H1N1 subtype currently included in licensed seasonal trivalent influenza vaccines, data suggest that children 6 months to 9 years of age are largely serologically naïve to the pandemic (H1N1) 2009 virus (MMWR 2009; 58(19) 521-524). Based on these data, children 9 years of age and younger should be administered 2 doses of the monovalent pandemic (H1N1) 2009 virus vaccine. Available data indicates that among adults some degree of pre-existing immunity to the pandemic (H1N1) 2009 virus exists, especially among those aged >60 years. Based on data from seasonal influenza vaccines we expect individuals 10 to 17 years of age to respond similarly to adults, so individuals 10 years of age and older should be administered 1 dose of monovalent pandemic (H1N1) 2009 virus vaccine. This dosing regimen, in which immunologically naïve persons receive 2 doses and primed individuals receive one dose is similar to that used for seasonal influenza vaccines.

Licensed unadjuvanted, monovalent pandemic (H1N1) 2009 vaccine would be labeled for use in the same populations as the respective seasonal trivalent vaccine. Thus, only those manufacturers with a currently licensed seasonal vaccine for use in children could obtain licensure of vaccine for active immunization against influenza disease caused by pandemic (H1N1) 2009 virus in that population.

III. REGULATORY PRECEDENT FOR LICENSURE OF A MONOVALENT VACCINE AS A STRAIN CHANGE SUPPLEMENT

Before 1978 influenza vaccines were monovalent and bivalent; since 1978, most US licensed influenza vaccines have been trivalent incorporating influenza A (H1N1), and A (H3N2) subtype viruses and an influenza B virus (*Fukuda, K., et al in Plotkin, Vaccines 4th Edition, Elsevier, p. 349*).

Monovalent vaccines have been licensed and distributed by FDA in the past; one such example was in 1986, when a supplemental monovalent influenza A H1N1 subtype (A/Taiwan/1/86) vaccine was licensed. Influenza A/Taiwan/1/86 H1N1 virus began to circulate among the human population in 1986. This virus represented a newly emerged antigenic variant of influenza A (H1N1) and was considered to be a significantly different influenza strain, relative to previous influenza A H1N1 virus isolates (*Robertson et al, J. gen. Virol. 68:1205-1208, 1987*). Influenza A/Tawain/1/86 H1N1 attack rates among individuals who had previously received seasonal trivalent influenza vaccine were not significantly different from rates among those who had not been vaccinated providing evidence that subjects had little prior immunity to this new vaccine strain. Furthermore, this virus affected a wider range of age groups and was poorly inhibited by antibodies induced by H1N1 strains circulating since 1977 (*Iorio eta al, Eur. J. Epid. 12:589-594, 1996, Teare et al, Brit. J. Gen. Prac, 40:10-12, 1990*). Despite these novel characteristics of influenza A/Taiwan/1/86 H1N1 virus, a monovalent influenza A/Taiwan/1/86 H1N1 virus vaccine was considered a strain change and was licensed as a supplemental vaccine

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following submission of an amendment (these are now supplements) to each manufacturer's license application for Influenza Virus Vaccine.

A search of archived files in FDA showed that Wyeth Laboratories amended its license application for "Influenza Virus Vaccine, Trivalent Types A and B" in November 1986 to include monovalent influenza A H1N1 subtype (A/Taiwan/1/86). This vaccine was marketed as "Influenza virus vaccine, monovalent, type A 1986-87 supplemental vaccine." Similarly, Connaught Laboratories (now Sanofi Pasteur) and Parke Davis amended their license applications (and FDA approved such amendments) for Influenza virus vaccine in October of 1986 to include monovalent A/Taiwan influenza vaccine strain as a supplemental vaccine for the 1986-87 season. Clinical data were not submitted to FDA concerning these supplemental vaccines.

IV. FDA GUIDANCE CONCERNING THE LICENSURE OF PANDEMIC VACCINES

FDA has issued guidance concerning the licensure of pandemic vaccines. To the extent that the strain change supplement approach to licensure is not specifically described in such guidance it is important to note the following distinctions between the current public health emergency (as declared under section 319 of the Public Health Service Act) concerning disease caused by pandemic (H1N1) 2009 virus and the factual assumptions behind previous FDA guidance. The FDA Guidance document "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) was intended to provide FDA's current thinking regarding criteria to evaluate the safety and effectiveness of influenza vaccines against potential pandemic strains. At the time this guidance was published (May 2007), disease caused by avian influenza A H5N1 subtype was of particular concern due to outbreaks in poultry and sporadic human infections. The H5N1 virus contains a hemagglutinin subtype that had not been isolated from humans prior to the emergence of human infections with the avian H5N1 influenza virus (*Lancet 1998; 351: 467-471, Lancet 1998; 351:472-477, Lancet 2004; 363: 617-619*). This hemagglutinin is thought to be responsible, at least in part, for the more severe disease as compared to disease caused by seasonal influenza viruses (*Gambotto et al. 2008 Lancet 371: 1464-1475*). One influenza A H5N1 vaccine manufactured by sanofi pasteur is licensed for use in the U.S. and is contained in the National Stockpile.

Because of the limited clinical experience with influenza A H5N1 subtype virus vaccines, the clinical evaluation of prospective adjuvanted and unadjuvanted H5N1 subtype vaccines was considered an essential component of preparedness. Thus, the focus of FDA's guidance in 2007 was on clinical development to facilitate and expedite the licensure of such vaccines for pandemic preparedness. In contrast to what has been observed with H5N1 influenza virus, epidemiologic data for pandemic (H1N1) 2009 virus indicate human-to-human spread and sustained community level outbreaks emphasizing the need to make a vaccine available as soon as possible. Furthermore, due to the similarities in influenza strain and subtype, as well as the use of the same manufacturing process for both the currently licensed seasonal influenza vaccines and the pandemic (H1N1) 2009 vaccines, it is scientifically valid to extrapolate the safety and

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effectiveness data supporting licensure of the seasonal vaccines to support approval of strain change supplements for the vaccines against pandemic (H1N1) 2009. In addition, licensure of a supplemental monovalent 2009 H1N1 is consistent with past regulatory actions as previously stated above. Because H1N1 vaccine strains have been incorporated in influenza vaccines for human use for decades, the regulatory pathway for licensure of the unadjuvanted, monovalent 2009 (H1N1) virus vaccine should follow that of seasonal H1N1 vaccines.

In addition, FDA's guidance entitled "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) suggests that submission of a BLA, as opposed to a BLA supplement, may be beneficial for the agency as it addresses trade name and labeling matters concerning the pandemic vaccine. These are important issues to be addressed; however, it is not the case that their resolution requires submission of a separate BLA. The proper names Influenza A (H1N1) 2009 Monovalent Vaccine and Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal have been assigned to these vaccines to distinguish them from the trivalent seasonal vaccines. In 1986 the supplemental vaccine was assigned a unique proper name (Influenza Virus Vaccine, Monovalent, Type A) to distinguish it from the licensed trivalent vaccine. Submission of a BLA supplement should not be an impediment to tracking and differentiating postmarketing adverse events for monovalent pandemic (H1N1) 2009 vaccine versus licensed trivalent vaccine. Post distribution surveillance for adverse events associated with monovalent vaccine use will be performed. Currently, the expectation is that events will be detected and evaluated using a number of systems including the Vaccine Adverse Event Reporting System (VAERS) to detect signals, as well as the Vaccine Safety Data (VSD) Link and collaborations with other data base systems such as the Department of Defense to detect signals and evaluate events associated with use.

Lastly, FDA's guidance on Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, (December 2004) commonly referred to as "the bundling policy" does not preclude the strain change supplement approach to the licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines by licensed manufacturers of seasonal influenza vaccines. This guidance was intended to explain what changes that required supporting clinical data could be grouped together in a single submission that would be assessed a single user fee as opposed to being reported in multiple submissions requiring multiple user fees. It also provides criteria to determine whether a change is more appropriately considered an efficacy supplement or a new application. The guidance does not appear to distinguish between efficacy supplements and Chemistry Manufacturing and Controls (CMC) supplements, which are not assessed a user fee. Supplements for strain changes to the seasonal Influenza vaccines have been, and continue to be, considered CMC supplements.

V. MEDIMMUNE'S INFLUENZA A (H1N1) 2009 MONOVALENT LIVE, INTRANASAL VACCINE

As described above, pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as included in the currently licensed seasonal trivalent influenza vaccine

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FluMist®. Unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine, licensed as a strain change, will be manufactured using the well-established, licensed egg-based manufacturing process by MedImmune. Influenza vaccines produced by this technology have an extensive track record of safety and effectiveness in the United States. Thus, the safety and effectiveness data derived from, and relating to, the FDA-approved BLA for Influenza Vaccine Live, Intranasal support licensure of an unadjuvanted, monovalent, pandemic (H1N1) 2009 vaccine produced by MedImmune. This data and information are included by reference in the BLA file pertaining to the licensure of MedImmune's Influenza A (H1N1) Monovalnet Vaccine Live, Intranasal.

EXHIBIT 2



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: September 15, 2009

To: File STN 103914/5260

From: Norman W. Baylor, PhD, *Norman W. Baylor*
Director, Office of Vaccines Research and Review (OVR)

Subject: Licensure of unadjuvanted, monovalent (H1N1) influenza virus vaccines for the 2009 H1N1 pandemic as a strain change supplement

Product: Influenza A (H1N1) 2009 Monovalent Vaccine

Manufacturer: Sanofi Pasteur, Inc.

I. INTRODUCTION

This memorandum summarizes the regulatory basis for FDA's approval of a supplement under Section 351 of the Public Health Service Act to Sanofi Pasteur biologics license application (BLA) for Influenza Virus Vaccine to include unadjuvanted, Influenza A (H1N1) 2009 Monovalent Vaccine for the 2009 pandemic.

II. REGULATORY FRAMEWORK FOR APPROVAL

II a. Regulatory Options:

The extent of global disease due to pandemic (H1N1) 2009 virus emphasizes the need for development and timely deployment of vaccine. FDA has considered applicable regulatory options to facilitate the licensure of unadjuvanted, monovalent vaccines against pandemic (H1N1) 2009 virus. These options only pertain to unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines manufactured using the same processes as used for currently U.S. licensed seasonal trivalent influenza vaccines and formulated to contain the same quantity of antigen as a single strain of the seasonal vaccine:

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- (i) BLA strain change supplement without clinical data at the time of submission. The immunogenicity data from ongoing clinical trials would be submitted post-licensure as a clinical efficacy supplement.
- (ii) BLA or BLA strain change supplement containing limited clinical data such as post-dose one immunogenicity data from on-going clinical studies. The post-dose 2 immunogenicity data would be submitted post-licensure.
- (iii) BLA with complete clinical dataset, i.e., submission of a BLA when clinical studies evaluating immunogenicity and safety following two doses of the 2009 H1N1 vaccine are completed.

OVRP discussed these options with FDA senior management including Drs. Margaret Hamburg, Jesse Goodman, Mary Lou Valdez and Murray Lumpkin on June 5, 2009. On July 10, 2009, representatives from FDA briefed staff from the Department of Health and Human Services (DHHS) and other Agencies within DHHS on these licensure issues during a meeting attended by, among others, HHS Chief of Staff Laura Petrou, ASPR Dr. Nicole Lurie, Dr. Bruce Gellin (NVPO) and Dr. Anthony Fauci (NIAID). FDA noted that in the case of an urgent public health need for a pandemic (H1N1) 2009 influenza vaccine, option (i) above, i.e., submission of a BLA strain change supplement without clinical data at the time of submission, provides the most expeditious regulatory pathway to licensure among the legally permissible options. Furthermore, this option is consistent with previous FDA regulatory decisions concerning influenza vaccines.

On July 23, 2009, FDA presented this licensure strategy to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) for discussion and received unanimous support from the VRBPAC members for licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 influenza vaccines as strain change supplements without clinical data.

II b. Characteristics of Pandemic (H1N1) 2009 Virus:

The pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as those present in currently licensed seasonal trivalent influenza vaccines. Influenza A virus H1N1 subtypes have circulated globally from at least the mid-1930s until 1957, reappeared in 1977 and have since caused influenza disease in the United States (*MMWR*, 1986; 35 (32); 517-21; *MMWR*, 2005; 54(RR-8):1-40).

Although pandemic (H1N1) 2009 viruses are antigenically distinct from previous seasonal influenza A (H1N1) human isolates, they are similar to classical swine A (H1N1) viruses and North American A (H1N1) viruses that circulated in swine in the US over the last decade, and that have occasionally infected humans during the same period (*Garten et al, Scienceexpress* /www.scienceexpress.org/ 22 May 2009/Page 1/10.1126/science.1176225). The pandemic (H1N1) 2009 virus does not present a change in influenza A subtype, even though it has a unique genome composition not identified previously, based on nucleotide sequencing and phylogenetic analysis. (*N Engl*

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J. Med 2009; 361, *N Engl. J. Med.* 10.1056/NEJMoa09038120; *N. Engl. J. Med* 2009; 361. DOI: 10.1056/NEJMoa0903810).

II c. Seasonal Influenza Vaccine Strain Change Supplements:

Gradual antigenic change in the influenza virus hemagglutinin (HA) and neuraminidase (NA) antigens requires annual assessment of influenza vaccine strains as well as annual administration of the seasonal trivalent influenza vaccine. Therefore, each year FDA and the VRBPAC consider the optimal strains for inclusion in the seasonal trivalent influenza vaccines. Following strain selection manufacturers submit strain change supplements to their license applications. Each new inactivated seasonal trivalent influenza vaccine (Influenza Virus Vaccine) made by currently licensed influenza vaccine manufacturers is licensed without additional clinical data specific for the new strain(s). Each new live seasonal trivalent influenza virus vaccine (Influenza Vaccine Live, Intranasal) is evaluated in approximately 300 individuals prior to approval to verify adequate attenuation. Safety and effectiveness of each new seasonal vaccine are extrapolated from data included in the approved license application as well as the post-marketing experience with preceding seasonal vaccines.

Approved dosing regimens for seasonal trivalent influenza vaccine for children and adults usually remain unchanged for strain change supplements and are based on clinical studies performed in the 1970s that demonstrated that children and adults unexposed to influenza either through natural infection or vaccination required two doses of inactivated vaccine to achieve acceptable antibody levels while persons with pre-existing immunity required a single dose (*Plotkin and Orenstein 4th edition, p. 350*). Moreover, among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (*Gross et al. J Clin Microbiol* 1987;25:1763-5. *Feery et al. Med J Aust* 1976;1:186, 188-9, and *Levine et al. CMAJ* 1987;137:722-6). This suggests that these individuals are immunologically primed to respond adequately to a single dose of vaccine formulated with an influenza subtype that is closely related to previously circulating subtypes..

II d. Unadjuvanted, Monovalent, Pandemic (H1N1) 2009 Virus Vaccines Strain Change Supplements:

Manufacturers of licensed seasonal trivalent influenza vaccines file a manufacturing strain change supplement to their existing BLA for the trivalent seasonal vaccine. The unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine will be manufactured using the licensed process and will be considered a strain change. Consistent with the data required for the seasonal vaccine strain change, clinical safety and immunogenicity data at the time of licensure will not be required for an inactivated unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine. For unadjuvanted, monovalent pandemic (H1N1) 2009 live virus vaccine, as is the case with the seasonal live attenuated influenza vaccine, limited clinical safety data will be provided prior to licensure. Safety and effectiveness of each monovalent vaccine is extrapolated from data included in the approved seasonal license application as well as the post-marketing experience with seasonal vaccines. Each strain change supplement for pandemic (H1N1) 2009 virus vaccine will reference the nonclinical, chemistry, manufacturing, and controls (CMC) information and clinical data in the original approved BLA for seasonal trivalent

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influenza vaccine. Sanofi Pasteur has initiated clinical studies with Influenza A (H1N1) 2009 Monovalent Vaccine to determine the optimal dosage, number of doses and schedule. These data will be submitted to their license application as a clinical efficacy supplement after approval of the strain change supplement.

Although pandemic (H1N1) 2009 virus belongs to the same influenza H1N1 subtype currently included in licensed seasonal trivalent influenza vaccines, data suggest that children 6 months to 9 years of age are largely serologically naïve to the pandemic (H1N1) 2009 virus (MMWR 2009; 58(19) 521-524). Based on these data, children 9 years of age and younger should be administered 2 doses of the monovalent pandemic (H1N1) 2009 virus vaccine. Available data indicate that among adults some degree of pre-existing immunity to the pandemic (H1N1) 2009 virus exists, especially among those aged >60 years. Based on data from seasonal influenza vaccines we expect individuals 10 to 17 years of age to respond similarly to adults, so individuals 10 years of age and older should be administered 1 dose of monovalent pandemic (H1N1) 2009 virus vaccine. This dosing regimen, in which immunologically naïve persons receive 2 doses and primed individuals receive one dose is similar to that used for seasonal trivalent influenza vaccines.

Licensed unadjuvanted, monovalent pandemic (H1N1) 2009 vaccine would be labeled for use in the same populations as the respective seasonal trivalent influenza vaccine. Thus, only those manufacturers with a currently licensed influenza vaccine for use in children could obtain licensure of vaccine for active immunization against influenza disease caused by pandemic (H1N1) 2009 virus in that population.

III. REGULATORY PRECEDENT FOR LICENSURE OF A MONOVALENT VACCINE AS A STRAIN CHANGE SUPPLEMENT

Before 1978 influenza vaccines were monovalent and bivalent; since 1978, most US licensed influenza vaccines have been trivalent incorporating influenza A (H1N1), and A (H3N2) subtype viruses and an influenza B virus (*Fukuda, K., et al in Plotkin, Vaccines 4th Edition, Elsevier, p. 349*).

Monovalent vaccines have been licensed and distributed by FDA in the past; one such example was in 1986, when a supplemental monovalent influenza A H1N1 subtype (A/Taiwan/1/86) vaccine was licensed. Influenza A/Taiwan/1/86 H1N1 virus began to circulate among the human population in 1986. This virus represented a newly emerged antigenic variant of influenza A (H1N1) and was considered to be a significantly different influenza strain, relative to previous influenza A H1N1 virus isolates (*Robertson et al, J. gen. Virol. 68:1205-1208, 1987*). Influenza A/Tawain/1/86 H1N1 attack rates among individuals who had previously received seasonal trivalent influenza vaccine were not significantly different from rates among those who had not been vaccinated providing evidence that subjects had little prior immunity to this new vaccine strain. Furthermore, this virus affected a wider range of age groups compared to previously circulating strains, and was poorly inhibited by antibodies induced by H1N1 strains circulating since 1977

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(*Iorio et al, Eur. J. Epid. 12:589-594, 1996, Teare et al, Brit. J. Gen. Prac, 40:10-12, 1990*). Despite these novel characteristics of influenza A/Taiwan/1/86 H1N1 virus, a monovalent influenza A/Taiwan/1/86 H1N1 virus vaccine was considered a strain change and was licensed as a supplemental vaccine following submission of an amendment (these are now supplements) to each manufacturer's license application for Influenza Virus Vaccine.

A search of archived files in FDA showed that Wyeth Laboratories amended its license application for "Influenza Virus Vaccine, Trivalent Types A and B" in November 1986 to include monovalent influenza A H1N1 subtype (A/Taiwan/1/86). This vaccine was marketed as "Influenza virus vaccine, monovalent, type A 1986-87 supplemental vaccine." Similarly, Connaught Laboratories (now Sanofi Pasteur) and Parke Davis amended their license applications (and FDA approved such amendments) for Influenza Virus Vaccine in October of 1986 to include monovalent A/Taiwan/1/86 influenza vaccine strain as a supplemental vaccine for the 1986-87 season. Clinical data were not submitted to FDA concerning these supplemental vaccines.

IV. FDA GUIDANCE CONCERNING THE LICENSURE OF PANDEMIC VACCINES

FDA has issued guidance concerning the licensure of pandemic influenza vaccines. To the extent that the strain change supplement approach to licensure is not specifically described in such guidance it is important to note the following distinctions between the current public health emergency (as declared under section 319 of the Public Health Service Act) concerning disease caused by pandemic (H1N1) 2009 virus and the factual assumptions behind previous FDA guidance. The FDA Guidance document "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) was intended to provide FDA's current thinking regarding criteria to evaluate the safety and effectiveness of influenza vaccines against potential pandemic strains. At the time this guidance was published (May 2007), disease caused by avian influenza A H5N1 subtypes was of particular concern due to outbreaks in poultry and sporadic human infections. The H5N1 virus contains a hemagglutinin subtype that had not been isolated from humans prior to the emergence of human infections with the avian H5N1 influenza virus (*Lancet 1998; 351: 467-471, Lancet 1998; 351:472-477, Lancet 2004; 363: 617-619*). This hemagglutinin is thought to be responsible, at least in part, for the more severe disease as compared to disease caused by seasonal influenza viruses (*Gambotto et al. 2008 Lancet 371: 1464-1475*). One influenza A H5N1 vaccine manufactured by sanofi pasteur is licensed for use in the U.S. and is contained in the National Stockpile.

Because of the limited clinical experience with influenza A H5N1 subtype virus vaccines, the clinical evaluation of prospective adjuvanted and unadjuvanted H5N1 subtype vaccines was considered an essential component of preparedness. Thus, the focus of FDA's guidance in 2007 was on clinical development to facilitate and expedite the licensure of such vaccines for pandemic preparedness. In contrast to what has been observed with H5N1 influenza virus, epidemiologic data for pandemic (H1N1) 2009 virus indicate human-to-human spread and sustained community level outbreaks

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emphasizing the need to make a vaccine available as soon as possible. Furthermore, due to the similarities in influenza subtype between the current and previously circulating H1N1 viruses, as well as the use of the same manufacturing process for both the currently licensed seasonal trivalent influenza vaccines and the pandemic (H1N1) 2009 vaccines, it is scientifically valid to extrapolate the safety and effectiveness data supporting licensure of the seasonal vaccines to support approval of strain change supplements for the vaccines against pandemic (H1N1) 2009 virus. In addition, licensure of a supplemental monovalent pandemic (H1N1) 2009 vaccine is consistent with past regulatory actions as previously stated above. Because H1N1 vaccine strains have been incorporated in influenza vaccines for human use for decades, the regulatory pathway for licensure of the unadjuvanted, monovalent pandemic (H1N1) 2009 vaccine should follow that of seasonal H1N1 vaccines.

In addition, FDA's guidance entitled "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) suggests that submission of a BLA, as opposed to a BLA supplement, may be beneficial for the agency as it addresses trade name and labeling matters concerning the pandemic vaccine. These are important issues to be addressed; however, it is not the case that their resolution requires submission of a separate BLA. The proper names Influenza A (H1N1) 2009 Monovalent Vaccine and Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal have been assigned to these vaccines to distinguish them from the seasonal trivalent influenza vaccines. In 1986 the supplemental vaccine was assigned a unique proper name (Influenza Virus Vaccine, Monovalent, Type A) to distinguish it from the licensed seasonal trivalent vaccine. Submission of a BLA supplement should not be an impediment to tracking and differentiating postmarketing adverse events for monovalent pandemic (H1N1) 2009 vaccine versus licensed seasonal trivalent influenza vaccine. Post distribution surveillance for adverse events associated with monovalent vaccine use will be performed. Currently, the expectation is that events will be detected and evaluated using a number of systems including the Vaccine Adverse Event Reporting System (VAERS) to detect signals, as well as the Vaccine Safety Data (VSD) Link and collaborations with other data base systems such as the Department of Defense to detect signals and evaluate events associated with use.

Lastly, FDA's guidance on Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, (December 2004) commonly referred to as "the bundling policy" does not preclude the strain change supplement approach to the licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines by licensed manufacturers of seasonal influenza vaccines. This guidance was intended to explain what changes that required supporting clinical data could be grouped together in a single submission that would be assessed a single user fee as opposed to being reported in multiple submissions requiring multiple user fees. It also provides criteria to determine whether a change is more appropriately considered an efficacy supplement or a new application. The guidance does not appear to distinguish between clinical efficacy supplements and Chemistry Manufacturing and Controls (CMC) supplements, which are not assessed a user fee. Supplements for strain changes to the seasonal trivalent influenza vaccines have been, and continue to be, considered CMC supplements.

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V. SANOFI PASTEUR'S INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE

As described above, pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as included in the currently licensed seasonal trivalent influenza vaccine Fluzone[®]. Unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine, licensed as a strain change, will be manufactured using the well-established, licensed egg-based manufacturing process by Sanofi Pasteur. Influenza vaccines produced by this technology have an extensive track record of safety and effectiveness in the United States. Thus, the safety and effectiveness data derived from, and relating to, the FDA-approved BLA for Influenza Virus Vaccine support licensure of an unadjuvanted, monovalent, pandemic (H1N1) 2009 vaccine manufactured by Sanofi Pasteur. These data and information are included by reference in the BLA file pertaining to the licensure of Sanofi Pasteur's Influenza A (H1N1) 2009 Monovalent Vaccine.

EXHIBIT 3



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: September 15, 2009

To: File STN 125254\127

From: Norman W. Baylor, PhD, *Norman W. Baylor*
Director, Office of Vaccines Research and Review (OVR)

Subject: Licensure of unadjuvanted, monovalent (H1N1) influenza virus vaccines for the 2009 H1N1 pandemic as a strain change supplement

Product: Influenza A (H1N1) 2009 Monovalent Vaccine

Manufacturer: CSL Limited

I. INTRODUCTION

This memorandum summarizes the regulatory basis for FDA's approval of a supplement under Section 351 of the Public Health Service Act to CSL Limited's biologics license application (BLA) for Influenza Virus Vaccine to include unadjuvanted, Influenza A (H1N1) 2009 Monovalent Vaccine for the 2009 pandemic.

II. REGULATORY FRAMEWORK FOR APPROVAL

II a. Regulatory Options:

The extent of global disease due to pandemic (H1N1) 2009 virus emphasizes the need for development and timely deployment of vaccine. FDA has considered applicable regulatory options to facilitate the licensure of unadjuvanted, monovalent vaccines against pandemic (H1N1) 2009 virus. These options only pertain to unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines manufactured using the same processes as used for currently U.S. licensed trivalent seasonal vaccines and formulated to contain the same quantity of antigen as a single strain of the seasonal vaccine:

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- (i) BLA strain change supplement without clinical data at the time of submission. The immunogenicity data from ongoing clinical trials would be submitted post-licensure as a clinical efficacy supplement.
- (ii) BLA or BLA strain change supplement containing limited clinical data such as post-dose one immunogenicity data from on-going clinical studies. The post-dose 2 immunogenicity data would be submitted post-licensure.
- (iii) BLA with complete clinical dataset, i.e., submission of a BLA when clinical studies evaluating immunogenicity and safety following two doses of the 2009 H1N1 vaccine are completed.

OVRP discussed these options with FDA senior management including Drs. Margaret Hamburg, Jesse Goodman, Mary Lou Valdez and Murray Lumpkin on June 5, 2009. On July 10, 2009, representatives from FDA briefed staff from the Department of Health and Human Services (DHHS) and other Agencies within DHHS on these licensure issues during a meeting attended by, among others, HHS Chief of Staff Laura Petrou, ASPR Dr. Nicole Lurie, Dr. Bruce Gellin (NVPO) and Dr. Anthony Fauci (NIAID). FDA noted that in the case of an urgent public health need for a pandemic (H1N1) 2009 influenza vaccine, option (i) above, i.e., submission of a BLA strain change supplement without clinical data at the time of submission, provides the most expeditious regulatory pathway to licensure among the legally permissible options. Furthermore, this option is consistent with previous FDA regulatory decisions concerning influenza vaccines.

On July 23, 2009, FDA presented this licensure strategy to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) for discussion and received unanimous support from the VRBPAC members for licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 influenza vaccines as strain change supplements.

II b. Characteristics of Pandemic (H1N1) 2009 Virus:

The pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as those present in currently licensed seasonal trivalent influenza vaccines. Influenza A virus H1N1 subtypes have circulated globally from at least the mid-1930s until 1957, reappeared in 1977 and have since caused influenza disease in the United States (*MMWR*, 1986; 35 (32); 517-21; *MMWR*, 2005; 54(RR-8):1-40).

Although pandemic (H1N1) 2009 viruses are antigenically distinct from previous seasonal influenza A (H1N1) human isolates, they are similar to classical swine A (H1N1) viruses and North American A (H1N1) viruses that circulated in swine in the US over the last decade, and that have occasionally infected humans during the same period (*Garten et al, Scienceexpress /www.scienceexpress.org/ 22 May 2009/Page 1/10.1126/science.1176225*). The pandemic (H1N1) 2009 virus does not present a change in influenza A subtype, even though it has a unique genome composition not identified previously, based on nucleotide sequencing and phylogenetic analysis. (*N Engl J. Med 2009; 361, N Engl. J. Med. 10.1056/NEJMoa09038120; N. Engl. J. Med 2009; 361. DOI: 10.1056/NEJMoa0903810*).

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II c. Seasonal Influenza Vaccine Strain Change Supplements:

Gradual antigenic change in the influenza virus hemagglutinin (HA) and neuraminidase (NA) antigens requires annual assessment of influenza vaccine strains as well as annual administration of the trivalent seasonal influenza vaccine. Therefore, each year FDA and the VRBPAC consider the optimal strains for inclusion in the seasonal trivalent vaccines. Following strain selection manufacturers submit strain change supplements to their license applications. Each new inactivated seasonal vaccine (Influenza Virus Vaccine) made by currently licensed influenza vaccine manufacturers is licensed without additional clinical data specific for the new strain(s). Each new live influenza virus vaccine (Influenza Vaccine Live, Intranasal) is evaluated in approximately 300 individuals prior to approval to verify adequate attenuation. Safety and effectiveness of each new seasonal vaccine are extrapolated from data included in the approved license application as well as the post-marketing experience with preceding seasonal vaccines. Approved dosing regimens for seasonal trivalent vaccine for children and adults usually remain unchanged for strain change supplements and are based on clinical studies performed in the 1970s that demonstrated that children and adults unexposed to influenza either through natural infection or vaccination required two doses of inactivated vaccine to achieve acceptable antibody levels while persons with pre-existing immunity required a single dose (*Plotkin and Orenstein 4th edition, p. 350*). Moreover, among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (*Gross et al. J Clin Microbiol 1987;25:1763-5. Feery et al. Med J Aust 1976;1:186, 188-9, and Levine et al. CMAJ 1987;137:722-6*). This suggests that these individuals are immunologically primed to respond adequately to a single dose of vaccine formulated with an influenza subtype that is closely related to previous subtypes..

II d. Unadjuvanted, Monovalent, Pandemic (H1N1) 2009 Virus Vaccines Strain Change Supplements:

Manufacturers of licensed seasonal influenza vaccines file a manufacturing strain change supplement to their existing BLA for the trivalent seasonal vaccine. The unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine will be manufactured using the licensed process and will be considered a strain change. Consistent with the data required for the seasonal vaccine strain change, clinical safety and immunogenicity data at the time of licensure will not be required for an inactivated unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine. For unadjuvanted, monovalent pandemic (H1N1) 2009 live virus vaccine, as is the case with the seasonal live attenuated influenza vaccine, limited clinical safety data will be provided prior to licensure. Safety and effectiveness of each monovalent vaccine is extrapolated from data included in the approved seasonal license application as well as the post-marketing experience with seasonal vaccines. Each strain change supplement for pandemic (H1N1) 2009 vaccine will reference the nonclinical, chemistry, manufacturing, and controls (CMC) information and clinical data in the original approved BLA for trivalent influenza vaccine. CSL Limited has initiated clinical studies with monovalent Influenza A (H1N1) 2009 Vaccine to determine the optimal dosage, number of doses and schedule. These data will be submitted to each

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license application as clinical efficacy supplements after approval of the strain change supplements.

Although pandemic (H1N1) 2009 virus belongs to the same influenza H1N1 subtype currently included in licensed seasonal trivalent influenza vaccines, data suggest that children 6 months to 9 years of age are largely serologically naïve to the pandemic (H1N1) 2009 virus (MMWR 2009; 58(19) 521-524). Based on these data, children 9 years of age and younger should be administered 2 doses of the monovalent pandemic (H1N1) 2009 virus vaccine. Available data indicates that among adults some degree of pre-existing immunity to the pandemic (H1N1) 2009 virus exists, especially among those aged >60 years. Based on data from seasonal influenza vaccines we expect individuals 10 to 17 years of age to respond similarly to adults, so individuals 10 years of age and older should be administered 1 dose of monovalent pandemic (H1N1) 2009 virus vaccine. This dosing regimen, in which immunologically naïve persons receive 2 doses and primed individuals receive one dose is similar to that used for seasonal influenza vaccines.

Licensed unadjuvanted, monovalent pandemic (H1N1) 2009 vaccine would be labeled for use in the same populations as the respective seasonal trivalent vaccine. Thus, only those manufacturers with a currently licensed seasonal vaccine for use in children could obtain licensure of vaccine for active immunization against influenza disease caused by pandemic (H1N1) 2009 virus in that population.

III. REGULATORY PRECEDENT FOR LICENSURE OF A MONOVALENT VACCINE AS A STRAIN CHANGE SUPPLEMENT

Before 1978 influenza vaccines were monovalent and bivalent; since 1978, most US licensed influenza vaccines have been trivalent incorporating influenza A (H1N1), and A (H3N2) subtype viruses and an influenza B virus (*Fukuda, K., et al in Plotkin, Vaccines 4th Edition, Elsevier, p. 349*).

Monovalent vaccines have been licensed and distributed by FDA in the past; one such example was in 1986, when a supplemental monovalent influenza A H1N1 subtype (A/Taiwan/1/86) vaccine was licensed. Influenza A/Taiwan/1/86 H1N1 virus began to circulate among the human population in 1986. This virus represented a newly emerged antigenic variant of influenza A (H1N1) and was considered to be a significantly different influenza strain, relative to previous influenza A H1N1 virus isolates (*Robertson et al, J. gen. Virol. 68:1205-1208, 1987*). Influenza A/Tawain/1/86 H1N1 attack rates among individuals who had previously received seasonal trivalent influenza vaccine were not significantly different from rates among those who had not been vaccinated providing evidence that subjects had little prior immunity to this new vaccine strain. Furthermore, this virus affected a wider range of age groups and was poorly inhibited by antibodies induced by H1N1 strains circulating since 1977 (*Iorio eta al, Eur. J. Epid. 12:589-594, 1996, Teare et al, Brit. J. Gen. Prac, 40:10-12, 1990*). Despite these novel characteristics of influenza A/Taiwan/1/86 H1N1 virus, a monovalent influenza A/Taiwan/1/86 H1N1

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virus vaccine was considered a strain change and was licensed as a supplemental vaccine following submission of an amendment (these are now supplements) to each manufacturer's license application for Influenza Virus Vaccine.

A search of archived files in FDA showed that Wyeth Laboratories amended its license application for "Influenza Virus Vaccine, Trivalent Types A and B" in November 1986 to include monovalent influenza A H1N1 subtype (A/Taiwan/1/86). This vaccine was marketed as "Influenza virus vaccine, monovalent, type A 1986-87 supplemental vaccine." Similarly, Connaught Laboratories (now Sanofi Pasteur) and Parke Davis amended their license applications (and FDA approved such amendments) for Influenza virus vaccine in October of 1986 to include monovalent A/Taiwan influenza vaccine strain as a supplemental vaccine for the 1986-87 season. Clinical data were not submitted to FDA concerning these supplemental vaccines.

IV. FDA GUIDANCE CONCERNING THE LICENSURE OF PANDEMIC VACCINES

FDA has issued guidance concerning the licensure of pandemic vaccines. To the extent that the strain change supplement approach to licensure is not specifically described in such guidance it is important to note the following distinctions between the current public health emergency (as declared under section 319 of the Public Health Service Act) concerning disease caused by pandemic (H1N1) 2009 virus and the factual assumptions behind previous FDA guidance. The FDA Guidance document "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) was intended to provide FDA's current thinking regarding criteria to evaluate the safety and effectiveness of influenza vaccines against potential pandemic strains. At the time this guidance was published (May 2007), disease caused by avian influenza A H5N1 subtype was of particular concern due to outbreaks in poultry and sporadic human infections. The H5N1 virus contains a hemagglutinin subtype that had not been isolated from humans prior to the emergence of human infections with the avian H5N1 influenza virus (*Lancet* 1998; 351: 467-471, *Lancet* 1998; 351:472-477, *Lancet* 2004; 363: 617-619). This hemagglutinin is thought to be responsible, at least in part, for the more severe disease as compared to disease caused by seasonal influenza viruses (*Gambotto et al. 2008 Lancet* 371: 1464-1475). One influenza A H5N1 vaccine manufactured by sanofi pasteur is licensed for use in the U.S. and is contained in the National Stockpile.

Because of the limited clinical experience with influenza A H5N1 subtype virus vaccines, the clinical evaluation of prospective adjuvanted and unadjuvanted H5N1 subtype vaccines was considered an essential component of preparedness. Thus, the focus of FDA's guidance in 2007 was on clinical development to facilitate and expedite the licensure of such vaccines for pandemic preparedness. In contrast to what has been observed with H5N1 influenza virus, epidemiologic data for pandemic (H1N1) 2009 virus indicate human-to-human spread and sustained community level outbreaks emphasizing the need to make a vaccine available as soon as possible. Furthermore, due to the similarities in influenza strain and subtype, as well as the use of the same manufacturing process for both the currently licensed seasonal influenza vaccines and the

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pandemic (H1N1) 2009 vaccines, it is scientifically valid to extrapolate the safety and effectiveness data supporting licensure of the seasonal vaccines to support approval of strain change supplements for the vaccines against pandemic (H1N1) 2009. In addition, licensure of a supplemental monovalent 2009 H1N1 is consistent with past regulatory actions as previously stated above. Because H1N1 vaccine strains have been incorporated in influenza vaccines for human use for decades, the regulatory pathway for licensure of the unadjuvanted, monovalent 2009 (H1N1) virus vaccine should follow that of seasonal H1N1 vaccines.

In addition, FDA's guidance entitled "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) suggests that submission of a BLA, as opposed to a BLA supplement, may be beneficial for the agency as it addresses trade name and labeling matters concerning the pandemic vaccine. These are important issues to be addressed; however, it is not the case that their resolution requires submission of a separate BLA. The proper names Influenza A (H1N1) 2009 Monovalent Vaccine and Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal have been assigned to these vaccines to distinguish them from the trivalent seasonal vaccines. In 1986 the supplemental vaccine was assigned a unique proper name (Influenza Virus Vaccine, Monovalent, Type A) to distinguish it from the licensed trivalent vaccine. Submission of a BLA supplement should not be an impediment to tracking and differentiating postmarketing adverse events for monovalent pandemic (H1N1) 2009 vaccine versus licensed trivalent vaccine. Post distribution surveillance for adverse events associated with monovalent vaccine use will be performed. Currently, the expectation is that events will be detected and evaluated using a number of systems including the Vaccine Adverse Event Reporting System (VAERS) to detect signals, as well as the Vaccine Safety Data (VSD) Link and collaborations with other data base systems such as the Department of Defense to detect signals and evaluate events associated with use.

Lastly, FDA's guidance on Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, (December 2004) commonly referred to as "the bundling policy" does not preclude the strain change supplement approach to the licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines by licensed manufacturers of seasonal influenza vaccines. This guidance was intended to explain what changes that required supporting clinical data could be grouped together in a single submission that would be assessed a single user fee as opposed to being reported in multiple submissions requiring multiple user fees. It also provides criteria to determine whether a change is more appropriately considered an efficacy supplement or a new application. The guidance does not appear to distinguish between efficacy supplements and Chemistry Manufacturing and Controls (CMC) supplements, which are not assessed a user fee. Supplements for strain changes to the seasonal Influenza vaccines have been, and continue to be, considered CMC supplements.

V. CSL LIMITED'S INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE

As described above, pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as included in the currently licensed seasonal trivalent influenza vaccine Afluria.

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Unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine, licensed as a strain change, will be manufactured using the well-established, licensed egg-based manufacturing process by CSL Limited. Influenza vaccines produced by this technology have an extensive track record of safety and effectiveness in the United States. Thus, the safety and effectiveness data derived from, and relating to, the FDA-approved BLA for Influenza Virus Vaccine support licensure of a unadjuvanted, monovalent, pandemic (H1N1) 2009 vaccine produced by CSL Limited. This data and information are included by reference in the BLA file pertaining to the licensure of CSL Limited's Influenza A (H1N1) 2009 Monovalent Vaccine.

EXHIBIT 4



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: September 15, 2009

To: File STN 103837/5514

From: Norman W. Baylor, PhD, *Norman W. Baylor*
Director, Office of Vaccines Research and Review (OVRR)

Subject: Licensure of unadjuvanted, monovalent (H1N1) influenza virus vaccines for the 2009 H1N1 pandemic as a strain change supplement

Product: Influenza A (H1N1) 2009 Monovalent Vaccine

Manufacturer: Novartis Vaccines and Diagnostics

I. INTRODUCTION

This memorandum summarizes the regulatory basis for FDA's approval of a supplement under Section 351 of the Public Health Service Act to Novartis Vaccines and Diagnostics' biologics license application (BLA) for Influenza Virus Vaccine to include unadjuvanted, Influenza A (H1N1) 2009 Monovalent Vaccine for the 2009 pandemic.

II. REGULATORY FRAMEWORK FOR APPROVAL

II a. Regulatory Options:

The extent of global disease due to pandemic (H1N1) 2009 virus emphasizes the need for development and timely deployment of vaccine. FDA has considered applicable regulatory options to facilitate the licensure of unadjuvanted, monovalent vaccines against pandemic (H1N1) 2009 virus. These options only pertain to unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines manufactured using the same processes as used for currently U.S. licensed trivalent seasonal vaccines and formulated to contain the same quantity of antigen as a single strain of the seasonal vaccine:

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- (i) BLA strain change supplement without clinical data at the time of submission. The immunogenicity data from ongoing clinical trials would be submitted post-licensure as a clinical efficacy supplement.
- (ii) BLA or BLA strain change supplement containing limited clinical data such as post-dose one immunogenicity data from on-going clinical studies. The post-dose 2 immunogenicity data would be submitted post-licensure.
- (iii) BLA with complete clinical dataset, i.e., submission of a BLA when clinical studies evaluating immunogenicity and safety following two doses of the 2009 H1N1 vaccine are completed.

OVRP discussed these options with FDA senior management including Drs. Margaret Hamburg, Jesse Goodman, Mary Lou Valdez and Murray Lumpkin on June 5, 2009. On July 10, 2009, representatives from FDA briefed staff from the Department of Health and Human Services (DHHS) and other Agencies within DHHS on these licensure issues during a meeting attended by, among others, HHS Chief of Staff Laura Petrou, ASPR Dr. Nicole Lurie, Dr. Bruce Gellin (NVPO) and Dr. Anthony Fauci (NIAID). FDA noted that in the case of an urgent public health need for a pandemic (H1N1) 2009 influenza vaccine, option (i) above, i.e., submission of a BLA strain change supplement without clinical data at the time of submission, provides the most expeditious regulatory pathway to licensure among the legally permissible options. Furthermore, this option is consistent with previous FDA regulatory decisions concerning influenza vaccines.

On July 23, 2009, FDA presented this licensure strategy to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) for discussion and received unanimous support from the VRBPAC members for licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 influenza vaccines as strain change supplements.

II b. Characteristics of Pandemic (H1N1) 2009 Virus:

The pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as those present in currently licensed seasonal trivalent influenza vaccines. Influenza A virus H1N1 subtypes have circulated globally from at least the mid-1930s until 1957, reappeared in 1977 and have since caused influenza disease in the United States (*MMWR*, 1986; 35 (32); 517-21; *MMWR*, 2005; 54(RR-8):1-40).

Although pandemic (H1N1) 2009 viruses are antigenically distinct from previous seasonal influenza A (H1N1) human isolates, they are similar to classical swine A (H1N1) viruses and North American A (H1N1) viruses that circulated in swine in the US over the last decade, and that have occasionally infected humans during the same period (*Garten et al, Scienceexpress /www.scienceexpress.org/ 22 May 2009/Page 1/10.1126/science.1176225*). The pandemic (H1N1) 2009 virus does not present a change in influenza A subtype, even though it has a unique genome composition not identified previously, based on nucleotide sequencing and phylogenetic analysis. (*N Engl J. Med* 2009; 361, *N Engl. J. Med.* 10.1056/NEJMoa09038120; *N. Engl. J. Med* 2009; 361. DOI: 10.1056/NEJMoa0903810).

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II c. Seasonal Influenza Vaccine Strain Change Supplements:

Gradual antigenic change in the influenza virus hemagglutinin (HA) and neuraminidase (NA) antigens requires annual assessment of influenza vaccine strains as well as annual administration of the trivalent seasonal influenza vaccine. Therefore, each year FDA and the VRBPAC consider the optimal strains for inclusion in the seasonal trivalent vaccines. Following strain selection manufacturers submit strain change supplements to their license applications. Each new inactivated seasonal vaccine (Influenza Virus Vaccine) made by currently licensed influenza vaccine manufacturers is licensed without additional clinical data specific for the new strain(s). Each new live influenza virus vaccine (Influenza Vaccine Live, Intranasal) is evaluated in approximately 300 individuals prior to approval to verify adequate attenuation. Safety and effectiveness of each new seasonal vaccine are extrapolated from data included in the approved license application as well as the post-marketing experience with preceding seasonal vaccines. Approved dosing regimens for seasonal trivalent vaccine for children and adults usually remain unchanged for strain change supplements and are based on clinical studies performed in the 1970s that demonstrated that children and adults unexposed to influenza either through natural infection or vaccination required two doses of inactivated vaccine to achieve acceptable antibody levels while persons with pre-existing immunity required a single dose (*Plotkin and Orenstein 4th edition, p. 350*). Moreover, among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (*Gross et al. J Clin Microbiol 1987;25:1763-5. Feery et al. Med J Aust 1976;1:186, 188-9, and Levine et al. CMAJ 1987;137:722-6*). This suggests that these individuals are immunologically primed to respond adequately to a single dose of vaccine formulated with an influenza subtype that is closely related to previous subtypes..

II d. Unadjuvanted, Monovalent, Pandemic (H1N1) 2009 Virus Vaccines Strain Change Supplements:

Manufacturers of licensed seasonal influenza vaccines file a manufacturing strain change supplement to their existing BLA for the trivalent seasonal vaccine. The unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine will be manufactured using the licensed process and will be considered a strain change. Consistent with the data required for the seasonal vaccine strain change, clinical safety and immunogenicity data at the time of licensure will not be required for an inactivated unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine. For unadjuvanted, monovalent pandemic (H1N1) 2009 live virus vaccine, as is the case with the seasonal live attenuated influenza vaccine, limited clinical safety data will be provided prior to licensure. Safety and effectiveness of each monovalent vaccine is extrapolated from data included in the approved seasonal license application as well as the post-marketing experience with seasonal vaccines. Each strain change supplement for pandemic (H1N1) 2009 vaccine will reference the nonclinical, chemistry, manufacturing, and controls (CMC) information and clinical data in the original approved BLA for trivalent influenza vaccine. Novartis Vaccines and Diagnostics has initiated clinical studies with monovalent Influenza A (H1N1) 2009 Vaccine to determine the optimal dosage, number of doses and schedule. These data will

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be submitted to each license application as clinical efficacy supplements after approval of the strain change supplements.

Although pandemic (H1N1) 2009 virus belongs to the same influenza H1N1 subtype currently included in licensed seasonal trivalent influenza vaccines, data suggest that children 6 months to 9 years of age are largely serologically naïve to the pandemic (H1N1) 2009 virus (MMWR 2009; 58(19) 521-524). Based on these data, children 9 years of age and younger should be administered 2 doses of the monovalent pandemic (H1N1) 2009 virus vaccine. Available data indicates that among adults some degree of pre-existing immunity to the pandemic (H1N1) 2009 virus exists, especially among those aged >60 years. Based on data from seasonal influenza vaccines we expect individuals 10 to 17 years of age to respond similarly to adults, so individuals 10 years of age and older should be administered 1 dose of monovalent pandemic (H1N1) 2009 virus vaccine. This dosing regimen, in which immunologically naïve persons receive 2 doses and primed individuals receive one dose is similar to that used for seasonal influenza vaccines.

Licensed unadjuvanted, monovalent pandemic (H1N1) 2009 vaccine would be labeled for use in the same populations as the respective seasonal trivalent vaccine. Thus, only those manufacturers with a currently licensed seasonal vaccine for use in children could obtain licensure of vaccine for active immunization against influenza disease caused by pandemic (H1N1) 2009 virus in that population.

III. REGULATORY PRECEDENT FOR LICENSURE OF A MONOVALENT VACCINE AS A STRAIN CHANGE SUPPLEMENT

Before 1978 influenza vaccines were monovalent and bivalent; since 1978, most US licensed influenza vaccines have been trivalent incorporating influenza A (H1N1), and A (H3N2) subtype viruses and an influenza B virus (*Fukuda, K., et al in Plotkin, Vaccines 4th Edition, Elsevier, p. 349*).

Monovalent vaccines have been licensed and distributed by FDA in the past; one such example was in 1986, when a supplemental monovalent influenza A H1N1 subtype (A/Taiwan/1/86) vaccine was licensed. Influenza A/Taiwan/1/86 H1N1 virus began to circulate among the human population in 1986. This virus represented a newly emerged antigenic variant of influenza A (H1N1) and was considered to be a significantly different influenza strain, relative to previous influenza A H1N1 virus isolates (*Robertson et al, J. gen. Virol. 68:1205-1208, 1987*). Influenza A/Tawain/1/86 H1N1 attack rates among individuals who had previously received seasonal trivalent influenza vaccine were not significantly different from rates among those who had not been vaccinated providing evidence that subjects had little prior immunity to this new vaccine strain. Furthermore, this virus affected a wider range of age groups and was poorly inhibited by antibodies induced by H1N1 strains circulating since 1977 (*Iorio eta al, Eur. J. Epid. 12:589-594, 1996, Teare et al, Brit. J. Gen. Prac, 40:10-12, 1990*). Despite these novel characteristics of influenza A/Taiwan/1/86 H1N1 virus, a monovalent influenza A/Taiwan/1/86 H1N1

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virus vaccine was considered a strain change and was licensed as a supplemental vaccine following submission of an amendment (these are now supplements) to each manufacturer's license application for Influenza Virus Vaccine.

A search of archived files in FDA showed that Wyeth Laboratories amended its license application for "Influenza Virus Vaccine, Trivalent Types A and B" in November 1986 to include monovalent influenza A H1N1 subtype (A/Taiwan/1/86). This vaccine was marketed as "Influenza virus vaccine, monovalent, type A 1986-87 supplemental vaccine." Similarly, Connaught Laboratories (now Sanofi Pasteur) and Parke Davis amended their license applications (and FDA approved such amendments) for Influenza virus vaccine in October of 1986 to include monovalent A/Taiwan influenza vaccine strain as a supplemental vaccine for the 1986-87 season. Clinical data were not submitted to FDA concerning these supplemental vaccines.

IV. FDA GUIDANCE CONCERNING THE LICENSURE OF PANDEMIC VACCINES

FDA has issued guidance concerning the licensure of pandemic vaccines. To the extent that the strain change supplement approach to licensure is not specifically described in such guidance it is important to note the following distinctions between the current public health emergency (as declared under section 319 of the Public Health Service Act) concerning disease caused by pandemic (H1N1) 2009 virus and the factual assumptions behind previous FDA guidance. The FDA Guidance document "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) was intended to provide FDA's current thinking regarding criteria to evaluate the safety and effectiveness of influenza vaccines against potential pandemic strains. At the time this guidance was published (May 2007), disease caused by avian influenza A H5N1 subtype was of particular concern due to outbreaks in poultry and sporadic human infections. The H5N1 virus contains a hemagglutinin subtype that had not been isolated from humans prior to the emergence of human infections with the avian H5N1 influenza virus (*Lancet* 1998; 351: 467-471, *Lancet* 1998; 351:472-477, *Lancet* 2004; 363: 617-619). This hemagglutinin is thought to be responsible, at least in part, for the more severe disease as compared to disease caused by seasonal influenza viruses (*Gambotto et al. 2008 Lancet* 371: 1464-1475). One influenza A H5N1 vaccine manufactured by sanofi pasteur is licensed for use in the U.S. and is contained in the National Stockpile.

Because of the limited clinical experience with influenza A H5N1 subtype virus vaccines, the clinical evaluation of prospective adjuvanted and unadjuvanted H5N1 subtype vaccines was considered an essential component of preparedness. Thus, the focus of FDA's guidance in 2007 was on clinical development to facilitate and expedite the licensure of such vaccines for pandemic preparedness. In contrast to what has been observed with H5N1 influenza virus, epidemiologic data for pandemic (H1N1) 2009 virus indicate human-to-human spread and sustained community level outbreaks emphasizing the need to make a vaccine available as soon as possible. Furthermore, due to the similarities in influenza strain and subtype, as well as the use of the same manufacturing process for both the currently licensed seasonal influenza vaccines and the

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pandemic (H1N1) 2009 vaccines, it is scientifically valid to extrapolate the safety and effectiveness data supporting licensure of the seasonal vaccines to support approval of strain change supplements for the vaccines against pandemic (H1N1) 2009. In addition, licensure of a supplemental monovalent 2009 H1N1 is consistent with past regulatory actions as previously stated above. Because H1N1 vaccine strains have been incorporated in influenza vaccines for human use for decades, the regulatory pathway for licensure of the unadjuvanted, monovalent 2009 (H1N1) virus vaccine should follow that of seasonal H1N1 vaccines.

In addition, FDA's guidance entitled "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" (May 2007) suggests that submission of a BLA, as opposed to a BLA supplement, may be beneficial for the agency as it addresses trade name and labeling matters concerning the pandemic vaccine. These are important issues to be addressed; however, it is not the case that their resolution requires submission of a separate BLA. The proper names Influenza A (H1N1) 2009 Monovalent Vaccine and Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal have been assigned to these vaccines to distinguish them from the trivalent seasonal vaccines. In 1986 the supplemental vaccine was assigned a unique proper name (Influenza Virus Vaccine, Monovalent, Type A) to distinguish it from the licensed trivalent vaccine. Submission of a BLA supplement should not be an impediment to tracking and differentiating postmarketing adverse events for monovalent pandemic (H1N1) 2009 vaccine versus licensed trivalent vaccine. Post distribution surveillance for adverse events associated with monovalent vaccine use will be performed. Currently, the expectation is that events will be detected and evaluated using a number of systems including the Vaccine Adverse Event Reporting System (VAERS) to detect signals, as well as the Vaccine Safety Data (VSD) Link and collaborations with other data base systems such as the Department of Defense to detect signals and evaluate events associated with use.

Lastly, FDA's guidance on Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, (December 2004) commonly referred to as "the bundling policy" does not preclude the strain change supplement approach to the licensure of unadjuvanted, monovalent pandemic (H1N1) 2009 vaccines by licensed manufacturers of seasonal influenza vaccines. This guidance was intended to explain what changes that required supporting clinical data could be grouped together in a single submission that would be assessed a single user fee as opposed to being reported in multiple submissions requiring multiple user fees. It also provides criteria to determine whether a change is more appropriately considered an efficacy supplement or a new application. The guidance does not appear to distinguish between efficacy supplements and Chemistry Manufacturing and Controls (CMC) supplements, which are not assessed a user fee. Supplements for strain changes to the seasonal Influenza vaccines have been, and continue to be, considered CMC supplements.

V. NOVARTIS VACCINES AND DIAGNOSTICS' INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE

Regulatory Memorandum September 15, 2009

As described above, pandemic (H1N1) 2009 virus belongs to the same influenza A H1N1 subtype as included in the currently licensed seasonal trivalent influenza vaccine Fluvirin®. Unadjuvanted, monovalent pandemic (H1N1) 2009 virus vaccine, licensed as a strain change, will be manufactured using the well-established, licensed egg-based manufacturing process by Novartis Vaccines and Diagnostics. Influenza vaccines produced by this technology have an extensive track record of safety and effectiveness in the United States. Thus, the safety and effectiveness data derived from, and relating to, the FDA-approved BLA for Influenza Virus Vaccine support licensure of a unadjuvanted, monovalent, pandemic (H1N1) 2009 vaccine produced by Novartis Vaccines and Diagnostics. This data and information are included by reference in the BLA file pertaining to the licensure of Novartis Vaccines and Diagnostics' Influenza A (H1N1) 2009 Monovalent Vaccine.

EXHIBIT 5

Health Care Personnel Influenza Vaccination Requirements

Effective Date: 8/13/09

Pursuant to the authority vested in the State Hospital Review and Planning Council and the Commissioner of Health by Public Health Law Sections 2803, 3612, and 4010, Title 10 (Health) of the Official Compilation of Codes, Rules and Regulations of the State of New York, is amended, to be effective upon filing with the Secretary of State, as follows:

Part 66 is amended to add Subpart 66-3, as follows:

Title: Subpart 66-3 – Health care facility personnel - influenza vaccination requirements

Sec.

66-3.1 Definitions

66-3.2 Health care facility – personnel influenza vaccination requirements

66-3.3 Health care facility requirements, existing personnel

66-3.4 Health care facility requirements, new personnel

66-3.5 Documentation

66-3.6 Exceptions

66-3.7 Reporting Requirements

Section 66 - 3.1 – Definitions

(a) "Medically contraindicated" means a physician licensed to practice in the State of New York or a nurse practitioner certified to practice in the State of New York certifies that influenza vaccine(s) should not be administered to an individual because it would be detrimental to the individual's health. Medical contraindication shall continue until such immunization is found no longer to be detrimental to the individual's health. Nationally recognized up-to-date guidance for medical contraindications and recommendations for vaccination(s) for influenza will be posted on the New York State Department of Health immunization page website and will be updated regularly.

(b) "Personnel" means all persons employed or affiliated with a healthcare facility, whether paid or unpaid, including but not limited to employees, members of the medical staff, contract staff, students, and volunteers, who either have direct contact with patients or whose activities are such that if they were infected with influenza, they could potentially expose patients, or others who have direct contact with patients, to influenza; provided, however, that the provisions of this subpart shall not apply to those individuals employed or affiliated with a facility that have neither direct contact with patients nor activities that could potentially expose patients or others who have direct contact with patients. This shall include, but not be limited to, any individual whose (i) job site is physically separated from patient care locations, and who has no direct contact with patients; and (ii) job activities would result in no more than infrequent and/or incidental direct contact with others who might have direct contact with patients; provided, that such direct contact is unlikely to transmit influenza. Examples include, but are not limited to, administrative, data entry, and building or property maintenance functions that meet the criteria of items (i) and (ii).

(c) "Health Care Facilities" include general hospitals as defined in section 2801 of the Public Health Law, diagnostic and treatment centers as defined in section 751.1 of part 751 of this Title, certified home health agencies, long term home health care programs, acquired immune deficiency syndrome (AIDS) home care programs and licensed home care services agencies as defined in section 3602 of the Public Health Law, and hospices as defined in section 4002 of the Public Health Law.

Section 66 - 3.2 – Health care facility - personnel influenza immunization requirements

Every health care facility in this state shall notify all personnel of the requirement and require that personnel be immunized against influenza virus(es) as a precondition to employment and on an annual basis. Such influenza vaccination(s) must be in accordance with the national recommendations in effect at the time of vaccination(s), unless the commissioner has determined that there is not an adequate supply of vaccine. If the commissioner determines the vaccine supplies are not adequate given the numbers of personnel to be vaccinated or vaccine(s) are not reasonably available, the commissioner may suspend the requirement(s) to vaccinate and/or change the annual deadline for such vaccination(s), as established in this subpart.

Section 66 - 3.3 – Health care facility requirements, existing personnel

Each health care facility must provide or arrange for influenza vaccination(s), at no cost to its personnel, either at the facility or elsewhere. Personnel may choose to receive influenza vaccination(s) from a source other than that arranged for by the facility and provide documentation to the facility as described in Section 66 – 3.5. Annual influenza vaccination(s) and the documentation thereof shall take place no later than November thirtieth of each year.

66 - 3.4 – Health care facility requirements, new personnel

Personnel newly entering into service at a facility after November thirtieth but before April first of each year shall have his or her status for influenza vaccination(s) determined by the facility and, if found to be deficient, the facility shall provide or arrange for the necessary vaccination(s) at no cost to the new personnel. Instead of obtaining influenza vaccination(s) from the facility, personnel may choose to receive influenza vaccination(s) from a source other than that arranged for by the facility and provide documentation as described in Section 66 – 3.5.

Section 66 - 3.5 - Documentation

The health care facility shall document the annual vaccination(s) against influenza virus of all personnel in their personnel files, including the date, site of administration, type of vaccine, dose, manufacturer and lot number of the vaccine, reactions if any, vaccine information statement given, and the name of the person administering the vaccines. If any personnel receive influenza vaccination(s) from other than facility staff, the facility shall document in the personnel file the date, type of vaccine, dose and name of the person administering the vaccine.

Section 66 – 3.6 - Exceptions

No personnel shall be required to receive an influenza vaccine if the vaccine is medically contraindicated for that individual. Nationally recognized up-to-date guidance for medical contraindications and recommendations for vaccination(s) for influenza will be posted on the New York State Department of Health immunization page website and will be updated regularly. The facility shall, on a case-by-case basis, evaluate what steps those who are not vaccinated pursuant to this section must take to reduce the risk of transmitting influenza to patients.

Section 66 - 3.7 - Reporting Requirements

Each facility shall collect aggregate data on personnel influenza vaccination(s) status for the period beginning April first and ending March thirty-first of each year and report that data to the department by May first of the same year in a manner determined by the commissioner. Required data will include, but not be limited to, number of personnel immunized by occupation, total number of personnel by occupation, and reason(s) personnel did not receive vaccine.

Subparagraph (v) of paragraph (10) of subdivision (b) of Section 405.3 of Part 405 is added to read as follows:

(v) documentation of preemployment and annual vaccination(s) against influenza, in accordance with Part 66 of this Title.

Paragraph (6) of subdivision (d) of Section 751.6 is added to read as follows:

(6) documentation of preemployment and annual vaccination(s) against influenza, in accordance with Part 66 of this Title.

Paragraph (5) of subdivision (c) of Section 763.13 is added to read as follows:

(5) documentation of preemployment and annual vaccination(s) against influenza, in accordance with Part 66 of this Title.

Paragraph (6) of subdivision (d) of Section 766.11 is added to read as follows:

(6) documentation of preemployment and annual vaccination(s), in accordance with Part 66 of this Title.

Paragraph (6) of subdivision (d) of Section 793.5 is added to read as follows:

(6) documentation of preemployment and annual vaccination(s) against influenza, in accordance with Part 66 of this Title.

REGULATORY IMPACT STATEMENT

Statutory Authority:

The authority for the promulgation of the regulatory changes adding Subpart 66-3 and amending Sections 405.3, 751.6, 766.11 and 793.5 of Title 10 is contained in Sections 2803 (2), 3612 and 4010 (4) of the Public Health Law (PHL). PHL section 2800 places the comprehensive responsibility for the development and administration of the state's policy with respect to Article 28 facilities with the State Department of Health. PHL Section 2803(2) authorizes the State Hospital Review and Planning Council (SHRPC) to adopt and amend rules and regulations, subject to the approval of the Commissioner, to implement the purposes and provisions of PHL Article 28, and to establish minimum standards governing the operation of health care facilities. PHL Section 3612 authorizes the SHRPC to adopt and amend rules and regulations, subject to the approval of the Commissioner, with respect to certified home health agencies, providers of long term home health care programs and providers of AIDS home care programs. PHL Section 4010 (4) authorizes the SHRPC to adopt and amend rules and regulations, subject to the approval of the Commissioner, with respect to hospice organizations.

Legislative Objectives:

The legislative objective of PHL Article 28 includes the protection of the health of the residents of the State by assuring the efficient provision and proper utilization of health services, of the highest quality at a reasonable cost. PHL Article 36 states a public commitment to the appropriate provision and expansion of services rendered to the residents of the State by certified home health agencies, to the maintenance of a consistently high level of services by all home care services agencies, to the central collection and public accessibility of information

concerning all organized home care services, and to the adequate regulation and coordination of existing home care services. PHL Article 40 declares that hospice is a socially and financially beneficial alternative to conventional curative care for those afflicted by terminal illness. In recognition of the value of hospice and consistent with State policy to encourage the expansion of health care service options available to New York State residents, it is the intention of the Legislature that hospice be available to all who seek such care and that it become a permanent component of the State's health care system. Immunizing staff of these providers against influenza will promote the health and safety of the patients they serve and support efficient provision of services.

Needs and Benefits:

The State Department of Health strongly advocates that all health care personnel (HCP) should receive annual influenza vaccination(s). This recommendation was communicated in two letters from the Commissioner (dated October 2006 and September 2007), and a health advisory (dated December 14, 2007), sent to hospitals, long term care facilities, providers and local health departments. PHL Article 21-A, the Long Term Care Resident and Employee Immunization Act, currently requires that all long-term care facilities, adult homes, adult day healthcare facilities, and enriched housing programs offer influenza vaccine to all employees and residents. Further amendments to PHL Article 21-A have been introduced to require all HCP under its purview to receive annual influenza vaccination(s).

The intent of this regulation is to coordinate the influenza vaccination requirements for personnel in Article 28, Article 36, and Article 40 entities to be the same; however, each type of

entity has a separate set of regulations that apply to them. In order to avoid the need to revise multiple regulations in the event of future changes to Subpart 66-3, the regulations for each type of provider entity will refer to one central set of requirements in Part 66. The authority for the Part 66-3 regulation, as applying to the affected types of facilities, rests with the State Hospital Review and Planning Council.

Each year, influenza causes significant morbidity and mortality in the United States, especially among the vulnerable populations in hospitals and long term care facilities. Common symptoms include the sudden onset of headache, high fever, cough, sore throat, fatigue and body aches. Complications of influenza may include bacterial or viral pneumonia; dehydration; the worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes; or death. The risk for complications, hospitalization, and death from influenza are higher among persons 65 years of age or older, young children, and persons with chronic medical conditions. Influenza is the sixth leading cause of death among adults in the United States, killing an average of 36,000 Americans annually and causing more deaths than all other vaccine-preventable diseases combined.

Influenza viruses spread mainly from person to person when an infected individual coughs or sneezes. Most healthy adults, including HCP, may be able to infect others beginning 1-2 days before symptoms develop and up to 5 days after becoming sick. That means HCP may be able to pass on the disease to a patient before they are aware they are sick or they may continue to work while they are contagious.

Influenza Infections in Hospitals and Long Term Care Facilities. Tables 1 and 2 detail the burden of nosocomial influenza infections (i.e., influenza infections acquired in hospitals and long term care facilities) in New York State by using NYSDOH surveillance data from 2001 to 2006. During the 2005-06 influenza season, there were 205 confirmed outbreaks in New York State hospitals and long-term care facilities. There were 1,896 suspected and confirmed cases of influenza associated with these reported outbreaks. As shown in Tables 1 and 2, the number of outbreaks and cases varies significantly year to year depending on the severity of that year's influenza season.

Table 1: Confirmed Influenza Outbreaks in New York State Hospitals and LTCFs

	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Total
Number of outbreaks reported to NYSDOH	31	173	24	199	451	205	70	1153

Source: NYSDOH surveillance data

Table 2: Morbidity from Nosocomial Influenza Infections in New York State

	2000-01*	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	Total
Number of patients/residents reported ill (suspected and confirmed) with nosocomial influenza in hospitals and LTCFs	359	2814	403	3535	8675	2603	663	19,052
Number of <u>staff</u> reported ill (suspected and confirmed) with nosocomial influenza in hospitals and LTCFs	55	889	146	1105	2124	702	158	5,179

Source: NYSDOH surveillance data

*Nosocomial data is only available from January 1, 2001 forward.

Role of HCP in Influenza Transmission. Influenza transmission and outbreaks in hospitals and nursing homes are well documented. HCP can acquire influenza from infected patients or the community and transmit influenza to patients and other staff. Many HCP develop no or only mild symptoms of the disease and, therefore, do not realize they have influenza and can transmit the disease to patients. Since influenza can be transmitted 1-2 days before the onset of symptoms, patients are at risk even if HCP do stay at home while ill.

A few studies provide estimates of the incidence of influenza-like illness among HCP. According to the CDC, “In one serosurvey of HCP, 23% had documented serologic evidence of influenza infection after a mild influenza season; however, of these, 59% could not recall having influenza, and 28% could not recall any respiratory infection, suggesting a high proportion of asymptomatic illness.” In addition, multiple studies have also shown that HCP continue to work despite being ill with influenza, increasing exposure of patients and coworkers. When HCP

come in to work while ill, whether it is because they do not want to lose sick time or pay or out of a sense of obligation, influenza virus can be transmitted to patients and other staff.

Studies have shown that influenza outbreaks in health facilities are associated with low vaccination rates among HCP and that, conversely, high vaccination rates among HCP are associated with fewer outbreaks. One study looked at the yearly incidence of lab-confirmed influenza illness among both staff and patients over 12 influenza seasons in an acute care facility, from 1999-2000. As the influenza vaccine rate climbed from 4% to 67%, the proportion of influenza cases decreased among hospitalized patients from 32% to 0, and among staff from 42% to 9%.

Influenza outbreaks in long-term care facilities are common and can cause severe outcomes in the vulnerable resident populations. Older adults in nursing homes often have multiple chronic or acute conditions that make them particularly susceptible to the complications of influenza disease. The intimate and constant care that is required by residents from the HCP who care for them allows for ready transmissibility from symptomatic or asymptomatic infected staff members. In addition, because influenza vaccination(s) is/are less effective among frail and elderly patients, outbreaks can occur in facilities where a high proportion of residents or patients are immunized. High vaccination levels of HCP are needed to protect patients, making influenza vaccination(s) of HCP an important patient safety issue.

A Scottish study compared mortality rates between long-term care hospitals that offered influenza vaccination to HCP, where 51% were vaccinated, and hospitals that did not, where

only 5% were vaccinated. The result was nearly a 40% reduction in all-cause mortality among the patients cared for by HCP in the hospitals with higher levels of HCP influenza vaccination.

Yet, despite the documented and positive effects of immunizing HCP against influenza on patient outcomes, HCP absenteeism, and reducing influenza infection among staff, and incentives to promote vaccination(s) of HCP, 30–50% continues to remain unvaccinated.

In 2000, New York State enacted Public Health Law Article 21-A requiring long-term care facilities to offer influenza vaccine to all residents and HCP and to document refusal of the vaccine. As seen in NYSDOH survey data, while the overall vaccination of residents has improved to 80% or greater in most facilities, the response among HCP has been poor (less than 45%).

CDC and National Recommendations. Recognizing the need to protect hospital patients and long-term care facility residents, the Centers for Disease Control and Prevention (CDC) has recommended influenza vaccination(s) for health care personnel (HCP) since 1981.

In November 2003, 24 leading organizations endorsed a policy to make annual influenza vaccination(s) among HCP an important goal for public health and safety. These organizations included the Society for Hospital Epidemiology of America, the American Medical Association, the American Academy of Family Practitioners, the American Academy of Pediatrics, and the American Nurses Association.

In February 2006, the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP) jointly recommended that all HCP be vaccinated annually against influenza.

In January 2007, the Infectious Disease Society of America called for a mandatory requirement for all HCP to receive influenza vaccination yearly.

Costs for the Implementation of and Continuing Compliance with these Regulations to the Regulated Entity

The cost to regulated entities to vaccinate personnel should be modest. Personnel in hospitals, diagnostic and treatment centers, home care services agencies and hospices all must undergo a health assessment to ensure that such personnel are free from a health impairment which is a potential risk to patients or which may interfere with the performance of his/her duties. Personnel are also required to have a certificate of vaccination against measles and rubella unless medically contraindicated and be tested for tuberculosis as condition of employment or affiliation. It should be noted that measles and rubella are one-time vaccinations, while influenza vaccination(s) is/are given annually. Many, if not most, facilities recognize the importance of their personnel receiving such vaccination(s) and already offer it to them, usually at no charge. Influenza vaccine is one of the least expensive vaccines and the average price in the private sector ranges from approximately \$9.75 to \$19.70 per dose.

Any additional costs to vaccinate all personnel should be more than offset by cost savings to the facility. Cost-effectiveness studies of adults aged <65 years indicate that vaccination(s) can reduce both direct medical costs and indirect costs from work absenteeism, resulting in 13%-

44% fewer health-care provider visits, 18%-45% fewer lost workdays, 18%-28% fewer days working with reduced effectiveness, and a 25% decrease in antibiotic use for influenza-like illness (ILI). HCP absenteeism can be a serious cause of staffing shortages during the influenza season at a time when emergency room visits and admissions due to influenza-related illness are greatly increased. The benefit of an immunized staff decreases direct and indirect costs to health care facilities.

Before 12/1/09, for inpatient hospital reimbursement, flu costs incurred prior to 12/1/09 may be the subject of a rate appeal per 10 NYCRR 86-1.17(a)(3). Section 86-1.17(a)(3) permits application for prospective revisions of certified rates and established revenue caps in the current year based on "[D]ocumented increases in the overall operating costs of a medical facility resulting from the implementation of additional or expanded programs, staff or services specifically mandated for the facility by the commissioner." After that time, the new hospital reimbursement system, PHL section 2807-c, subdivision 35 (added by section 2 of Part C, Chapter 58 of the Laws of 2009) permits very limited rate appeals, as noted in PHL 2807-c (35)(b)(x).

Reimbursement for certified home health agencies (CHHA) is set forth in 10 NYCRR 86-1.46. This is not impacted by the new subdivision 35. Consequently, CHHA rate appeals based on new DOH mandated services may continue to be available.

For long-term home health care programs, reimbursement is found in Subpart 86-5 of 10 NYCRR and section 86-5.14(a)(3) and permits the commissioner to consider applications for revision of certified rates which are based on "significant increases in the overall

operating costs of the long term home health care program resulting from the implementation of additional programs, staff or services specifically mandated for the program by the commissioner."

Diagnostic and treatment centers (D&TC) rates were scheduled to move to a new system (APGs) on March 1, 2009, but the transition has not occurred due to a delay in federal approval of state plan amendments. In the interim, 10 NYCRR 86-4.16(c) would continue to permit D&TC rate appeals based on new mandates.

Cost to State and Local Government:

The regulatory requirements are not expected to result in costs to state or local governments. Potential savings to Medicaid and other payors are expected by decreasing influenza cases. Among healthy persons aged 18-64 years, vaccination(s) can save an estimated \$60-\$4,000 per illness, depending on the cost of vaccination(s), the influenza attack rate, and vaccine effectiveness against influenza-like illness (ILI). In another economic analysis, vaccination(s) resulted in an average annual cost savings of \$13.66 per person vaccinated; however, other analyses have not demonstrated cost savings. Among studies of healthy young adults, >70% of the costs prevented were associated with reductions in lost work productivity. The estimated annual direct cost of influenza infection in the United States is estimated to be between 3 and 5 billion dollars.

In the event that medical facilities and long-term home health care programs seek a timely medicaid rate change and it is approved, the state and local government may have to pay a proportion of the amount approved, with the federal government contributing the balance.

However, due to the medicaid cap imposed on the county share, it is impossible at this time to calculate whether local governments will in fact have to contribute any funds to meet this potential expense.

Cost to the Department of Health:

Minimal new costs to the New York State Department of Health {NYSDOH} will be incurred associated with enactment of these regulations. By decreasing HCP influenza disease and absenteeism, and the spread of influenza disease among patients, the quality of health care should be improved, as well as patient outcomes.

NYSDOH has dedicated multiple resources to promote voluntary HCP vaccination(s) programs in public health and private arenas, including hospitals, clinics, and local health organizations over the past decade. As previously mentioned, the standard for care in New York State is that all HCP should receive annual influenza vaccination(s). This recommendation was sent to all New York State hospitals, long-term care facilities, providers and local health departments, via two Commissioner letters (dated October 2006 and September 2007), and a Health Advisory (December 14, 2007). Other initiatives to promote this practice have included educational materials, toolkits, a department-wide workgroup, outreach to healthcare partners, and public service announcements. These initiatives will continue.

Any additional costs will be associated with increased oversight of compliance with the regulatory requirements. NYSDOH already collects data from long-term care facilities on an annual basis to monitor compliance with PHL Article 21-A. Long-term care facilities must submit an annual report (DOH form 4193) to NYSDOH by May 1 providing information on the

number of residents and employees who received and the number who did not receive influenza and pneumococcal vaccine during the previous year. This form will be modified to capture data from additional health care facilities. Additional costs will mostly involve the additional data collection, analysis, written reports and follow-up with facilities.

Local Government Mandates:

There are no local government mandates in New York State related to this proposal, except as they apply to providers operated by local government entities.

Paperwork:

PHL Article 21-A, the New York State Long-Term Care Resident and Employee Immunization Act, requires nursing homes, adult care facilities, enriched housing facilities, and adult day health care programs in New York State to document their vaccination efforts and to submit an annual report to NYSDOH. The facility annual report was historically completed using DOH form 4193. This form is now available on the Health Provider Network (HPN). The form will be modified to capture hospitals, diagnostic and treatment centers, home care and hospice programs. Those entities covered by these regulations will be required to submit vaccination information using the Health Commerce System. All reporting will be accomplished using the internet only.

Duplication:

This proposal does not duplicate any state or federal regulation.

Alternative Approaches:

Voluntary programs to increase HCP influenza vaccination rates have not resulted in adequate vaccination levels. For the past decade, the New York State Department of Health has dedicated multiple resources to promote voluntary HCP vaccination programs in public health and private arenas, including hospitals, clinics, and local health organizations. Initiatives have included educational materials, toolkits, a department-wide workgroup, outreach to healthcare partners, and public service announcements. However, these programs have failed to substantially increase HCP vaccination rates.

On April 1, 2000, Article 21-A, the Long-Term Care Resident and Employee Immunization Act, was added to the Public Health Law. This law requires nursing homes, adult homes, enriched housing programs, and adult day health care programs to provide or arrange for influenza vaccination(s) for all residents and employees every year. The law also requires these types of facilities to provide or arrange for pneumococcal vaccination(s) for all residents and employees for whom the vaccine is recommended according to guidelines issued by the Advisory Committee on Immunization Practices. Residents and employees may refuse vaccination(s) due to medical contraindication, religious objection, or by choice after being fully informed of the health benefits and risks of such action. These long-term care facilities must document vaccination status of residents and employees, including refusal of vaccination(s) and the reasons for refusal.

In 2001, NYSDOH began collecting data from long-term care facilities to monitor compliance with PHL Article 21-A. Long-term care facilities must submit an annual report

(DOH form 4193) to NYSDOH by May 1 providing information on the number of residents and employees who received and the number that did not receive influenza and pneumococcal vaccine during the previous year. Even the enactment of NYS PHL Article 21-A targeting long-term care facilities has failed to promote consistent HCP vaccination rates above 44%.

A requirement for vaccination(s) is not unique to influenza. Childhood vaccination rates vastly improved in the US, often exceeding 90–95%, once mandatory school-entry vaccination requirements were put into place. In health care settings, measles and rubella vaccination has also been successful in achieving nearly universal vaccination of health employees against these pathogens. Consequently, requiring influenza vaccination(s) for health care workers would similarly be highly effective and, perhaps with additional education, widely accepted.

Federal Requirements:

There are no minimum standards established by the federal government for the same or similar subject areas.

Compliance Schedule:

This proposal will go into effect upon filing with the Secretary of State.

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REGULATORY FLEXIBILITY ANALYSIS
FOR SMALL BUSINESS AND LOCAL GOVERNMENTS

Effect of Rule:

Any facility defined as a hospital pursuant to PHL Article 28, as a home care services agency by PHL Article 36, or hospice by PHL Article 40 will be required to comply. Small businesses (defined as 100 employees or less), independently owned and operated, affected by this rule will include: 3 hospitals, 237 diagnostic and treatment centers, 91 nursing homes, 252 certified home health agencies, and approximately 900 licensed home care services agencies. There are 50 certified hospices in New York State; most of them would fit into the category of a small business, but definitive data concerning their small business status is not available.

Compliance Requirements:

All facilities must document the preemployment and annual vaccination(s) for influenza virus, subject to the availability of an adequate supply of the necessary vaccine and subject to exemptions for medical contraindications.

Professional Services:

Facilities will need to provide or arrange for influenza vaccination(s) of personnel. Most facilities currently offer influenza vaccinations to their personnel on a voluntary basis. It is not anticipated that facilities will need to hire additional staff to meet this mandate.

Compliance Costs:

The cost to facilities to meet this mandate is estimated to be minimal. It is anticipated that any costs incurred to vaccinate HCP will be offset by savings in direct medical costs by reducing influenza infection among HCP and patients, as well as savings in indirect costs associated with HCP absenteeism.

Economic and Technological Feasibility:

This proposal is economically and technically feasible.

Minimizing Adverse Impact:

There are no alternatives to the proposal to require influenza vaccination(s) of all HCP.

Small Business and Local Government Participation:

Outreach to the affected parties has been conducted. Such parties include professional organizations representing physicians, nurses, and other health care personnel, as well as general hospitals, diagnostic and treatment centers, home care agencies and hospices.

The organization representing county health officers, NYSACHO, has also been briefed. Organizations that represent the affected parties are given notice of this proposal by its inclusion on the agenda of the Codes and Regulations Committee of the State Hospital Review and Planning Council (SHRPC).

Presentations by Department staff were also given at the full Public Health Council and State Hospital Review and Planning Council meetings to brief Council members on this

upcoming proposal. The public, including many affected parties, have been in attendance at these meetings.

RURAL AREA FLEXIBILITY ANALYSIS

Pursuant to section 202-bb of the State Administrative Procedure Act (SAPA), a rural area flexibility analysis is not required. These provisions apply uniformly throughout New York State, including all rural areas.

The proposed rule will not impose an adverse economic impact on rural facilities defined within PHL Articles 28, 36, or 40. It will require additional documentation, record-keeping and other compliance requirements on public or private entities, but it is not expected to adversely affect rural areas.

JOB IMPACT STATEMENT

A Job Impact Statement is not included in accordance with Section 201-a (2) of the State Administrative Procedure Act (SAPA), because it will not have a substantial adverse effect on jobs and employment opportunities.

EMERGENCY ADOPTION JUSTIFICATION

Transmission of influenza disease from health care personnel to patients is a serious and significant patient safety issue because influenza disease is a leading cause of morbidity and mortality among hospitalized patients and those admitted to other types of health care facilities. This fact, plus the new threat posed to health and safety by the novel H1N1 influenza A strain that is circulating in New York State, puts a need for emergency regulations requiring that all health care personnel (HCP) be immunized against influenza annually into focus for the upcoming influenza season. Yearly, a significant threat to the health of patients, HCP themselves, and local communities exists that will be magnified in the upcoming season by the ongoing pandemic. The sooner that the emergency regulations are in place the sooner lives will be saved and other complications of influenza disease avoided.

Each year, influenza causes significant morbidity and mortality in the United States, especially among the vulnerable populations in hospitals and other health care facilities. Complications of influenza may include bacterial or viral pneumonia; dehydration; the worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes; or death. The risk for complications, hospitalization, and death from influenza are higher among persons 65 years of age or older, young children, and persons with chronic medical conditions. Influenza is the sixth leading cause of death among adults in the United States, killing an average of 36,000 Americans annually and causing more deaths than all other vaccine-preventable diseases combined.

Recognizing the need to protect patients, the Centers for Disease Control and Prevention (CDC) has recommended influenza vaccination for HCP since 1981. In February 2006, the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory

Committee on Immunization Practices (ACIP) jointly recommended that all HCP be vaccinated annually against influenza. In addition, the Infectious Disease Society of America, the Society of Hospital Epidemiologist of America, the American Medical Association, the American Academy of Family Practitioners, the American Academy of Pediatrics, the Association of Perioperative Nurses, the American Nurses Association, and multiple individual health care institutions have all supported and called for all HCP to receive influenza immunization yearly. Facilities that employ HCP have been strongly encouraged to provide vaccine to their staff by using evidence-based approaches that maximize the use of influenza vaccination.

Yet, despite the documented and positive effects of immunizing HCP against influenza on patient outcomes, HCP absenteeism, and reducing influenza infection among staff, and the fact that influenza transmission and outbreaks in healthcare facilities are well documented, national vaccination coverage rates among HCP continue to remain low, at around 42%. Even among health care centers utilizing highly organized and aggressive campaigns and incentives to promote immunization of HCP, 30–50% continue to remain unvaccinated. In 2000, New York State enacted Public Health Law Article 21A requiring long term care facilities to offer influenza vaccine to all residents and HCP and to document refusal of the vaccine. As seen in New York State Department of Health (NYSDOH) survey data, while the overall vaccination of residents has improved to 80% or greater in most facilities, the response among HCP has been poor.

Because of the serious consequences of nosocomial influenza outbreaks, as well as the impact on health care workers and the economic impact on health care systems, it is imperative that action be taken to ensure high health care worker vaccination rates. HCP absenteeism can result in serious staffing shortages during the influenza season, at a time when emergency room visits and admissions due to influenza-related illness are greatly increased. The benefit of an immunized staff decreases direct and indirect costs to health care facilities. The United States

and New York State are entering the 2009-2010 influenza season this Fall facing an emergency situation, with the potential circulation of both seasonal influenza viruses and the pandemic novel H1N1 influenza strain. Health care resources will be strained to the breaking point while addressing the burden of treating large numbers of patients ill with influenza. HCP need to be protected so that they will not become ill, transmit influenza to patients, their families and their communities, and also so that the health care system can be preserved and not collapse due to high degrees of HCP absenteeism. The urgency of this situation necessitates immediate emergency regulatory action to allow sufficient time for hospitals to arrange for the purchase and administration of influenza vaccine for the upcoming influenza season. This will also give health care facilities time to prepare for an extended novel H1N1 influenza vaccination campaign, in tandem with seasonal vaccination efforts.

Immunizing the staff of health care facilities against influenza will promote the health and safety of the patients they serve and support efficient provision of services during the pandemic. The NYSDOH has strongly and continuously advocated that all HCP should receive annual influenza vaccination(s). Annual influenza morbidity and mortality necessitates requiring influenza vaccination of all HCP in hospitals and other health care facilities on an emergency basis, so that lives can be saved. This is an even more urgent imperative during the current novel H1N1 influenza pandemic.

Summary of Key Points

- The burden of influenza disease is very high in health care facilities and will increase due to the current pandemic.

- Influenza vaccination of HCP is a patient and community safety issue and protects vulnerable hospitalized patients during seasonal influenza seasons and during the pandemic.
- HCP need to be vaccinated to control influenza in health care facilities even if patient vaccination rates are high.
- During the pandemic, it may be recommended that HCP receive influenza vaccination as the first line of protection of the public.
- Seasonal and pandemic influenza vaccination can be cost saving to health care facilities by decreasing absenteeism, improving patient outcomes, decreasing error rates, increasing quality of care, and decreasing personal and organizational expenditures.
- Voluntary programs to increase HCP influenza immunization rates have not resulted in adequate immunization levels.

EXHIBIT 6

ORIGINAL

STATE OF NEW YORK
COUNTY OF ALBANY

ALBANY SUPREME COURT

**LORNA PATTERSON, RN, KATHRYN DUPUIS, RN,
STEPHANIE GOERTZ, RN and JOHN DOE
and JANE DOE, being fictitious names representing
persons similarly situated,**

Petitioners,

**ORDER TO SHOW
CAUSE**

-against-

Index No. 8830-09

**RICHARD F. DAINES, in his official capacity as
Commissioner of the New York State Department of
Health, JEFFREY A. KRAUT, in his official Capacity
as Chair of the New York State Hospital Review
and Planning Council,**

Respondents.

Upon the annexed Petition, verified the 14th day of October, 2009, and the exhibits annexed thereto, and the affidavits of Petitioners Lorna Patterson, RN, Kathryn Dupuis, RN and Stephanie Goertz, RN, dated October 14th, 2009:

IT IS ORDERED that Respondents show cause at a term of this court, to be held at the Supreme Court, Albany County, Room 128, 16 Eagle Street, Albany, New York, 12207, on the 30 day of October 2009 in the forenoon, or as soon thereafter as counsel can be heard, why judgment of prohibition should not issue forthwith, prohibiting Respondents from enforcing "Health Care Personnel Influenza Vaccination Requirements," 10 NYCRR 66-3, and it is further

ORDERED, that a temporary restraining order is hereby granted restraining Respondents from enforcing th August 2009 amended regulation (Title 10 NYCRR 66-3) pending a hearing and

determination on the merits, and it is further

COUNTY

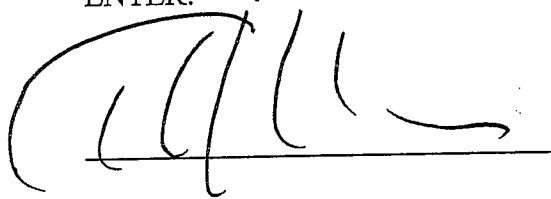
ORDERED that service of a copy of this Order to Show Cause and the papers upon which it is based shall be deemed good and sufficient service if made by regular mail and facsimile delivered to each Respondent on or before the 20 day of October 2009 and it is further

ORDERED that answering papers, if any, shall be served so as to arrive at the offices of Petitioners' attorney, Terence L. Kindlon, Esq., Kindlon Shanks and Associates, 74 Chapel Street, Albany, New York 12207, no later than the 29 day of Oct, 2009, by 1:30 ~~pm~~ afternoon and Petitioners' reply papers shall be served and filed on or before the return date.

Dated: 10/12, 2009

Albany, New York

ENTER:



Hon. THOMAS MCNAMARA

ACTING SUPREME COURT JUSTICE

EXHIBIT 7



Corning Tower The Governor Nelson A. Rockefeller Empire State Plaza Albany, New York 12237

Richard F. Daines, M.D.
Commissioner

James W. Clyne, Jr.
Executive Deputy Commissioner

October 23, 2009

Dear Administrator:

In August 2009 the State Hospital Review and Planning Council (SHRPC) adopted on an emergency basis 10 NYCRR Subpart 66-3, requiring certain health care facility personnel to be vaccinated with influenza vaccines. I am writing to inform you of my determination pursuant to Section 66-3.2 of those regulations that supplies of seasonal and 2009 H1N1 influenza vaccines are not adequate and that such vaccines are not reasonably available. Therefore, I hereby suspend the requirement for the health care personnel to be vaccinated against both influenza viruses for the current influenza season (through April 1, 2010).

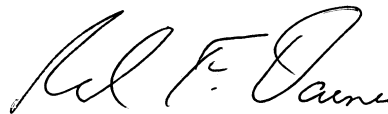
On October 14, 2009, the Centers for Disease Control and Prevention (CDC) issued an update on the availability of the 2009 trivalent seasonal influenza vaccine. According to the CDC, 114 million doses of seasonal vaccine will be brought to market in the U.S. The CDC update stated that "Because the total number of doses that will be made this year is approximately the same as the number of doses that were actually administered last year, an increase in demand cannot be met this season." The Department of Health (DOH) has received numerous calls from hospitals, other regulated facilities, county health departments and members of the public about difficulty in obtaining seasonal influenza vaccine. The national vaccine ordering website indicates that the major influenza vaccine distributors have little or no vaccine available to order. According to the CDC, manufacturers are not able to produce additional 2009 seasonal influenza vaccine.

Supplies of monovalent 2009 H1N1 influenza vaccine have become available from the federal government in the last three weeks. Federal planning scenarios for H1N1 vaccination programs at the time SHRPC adopted Subpart 66-3 showed that 120 million doses of vaccine would be available by the end of October and 200 million doses would be available by the end of November, almost twice the number of doses of seasonal vaccine usually administered. More concrete projections, made available by CDC just prior to the opening of the federal H1N1 vaccine ordering and distribution program, estimated a total of 52.5 million doses available by October 30 and 84.9 million doses available by November 27. However, as of this date, CDC is estimating only 27.7 million doses available by October 30 and 65.9 million doses by November 27, representing a 47% and 22% reduction respectively.

These circumstances set up a dynamic where health care personnel covered under the regulation might compete for vaccine with persons with underlying risk factors for adverse outcome of influenza infection. In a situation where the choice to vaccinate is between health care personnel and persons at risk, I have always held that patients take precedence. Maintaining the health care personnel vaccination requirement would delay persons in need from being vaccinated. For these reasons, I have determined that there will not be sufficient supplies of either vaccine to meet the intent of the regulation in the 2009-2010 influenza season.

The most important consideration driving the need for the regulation requiring health care personnel influenza vaccination is patient safety. Patients in hospitals and other health care settings have the right to expect that they will not be infected by their health care worker with a preventable disease which could be fatal. I believe that New York's experience with mandatory influenza vaccination for health care personnel in 2009 will have a positive impact on the health of New Yorkers this year. The current emergency regulation mandating influenza vaccinations for health care workers will expire on November 11, 2009, and a second emergency regulation would not have the desired effect during the current H1N1 influenza season or the expected seasonal outbreaks expected later this year and in early 2010. Therefore, no new emergency regulations will be promulgated. Instead, the DOH is advancing a permanent regulation requiring health care personnel in these settings to be vaccinated. Draft regulations will be published soon for a period of public comment.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard F. Daines". The signature is fluid and cursive, with the first name "Richard" being the most prominent.

Richard F. Daines, M.D.
Commissioner of Health