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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF ALAMEDA

CINDY KIEL, J.D., an Executive Associate Vice Chancellor at UC Davis, MCKENNA HENDRICKS, a UC Santa Barbara student, EDGAR DE GRACIA, a UCLA student, and LELAND VANDERPOEL, an employee at the Fresno satellite extension of the UCSF Medical Education Program,

Plaintiffs,

vs.

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, a Corporation, and MICHAEL V. DRAKE, in his official capacity as President of the UNIVERSITY OF CALIFORNIA,

Defendants.

CASE NO.

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

ASSIGNED FOR ALL PURPOSES TO:
JUDGE
DEPARTMENT

UNLIMITED CIVIL JURISDICTION

Plaintiffs by their undersigned counsel hereby allege against the Defendants as follows:

INTRODUCTION

1. This case challenges the Executive Order issued by former UC System President Janet Napolitano on July 31, 2020, mandating the flu vaccine for all students, faculty, and employees by November 1, 2020 as a condition of continued employment and continued school enrollment for students.[1]

2. There are three reasons why the EO must be struck down. First, it was issued in violation of the UC governance documents and shared governance principles requiring formal consultation with the Faculty Senate.

3. Second, the EO is unconstitutional because it compels the 510,000-member community to vaccinate against the flu, which has no proven benefit against COVID-19. As a result, the actual justification for the flu vaccine mandate boils down to mitigating a possible future shortage of hospital beds, if there is a second wave, and if there is a big seasonal flu outbreak, and if as a result, there would be a shortage of hospital beds.[2]

4. Constitutionally, there are just too many "ifs" to force 510,000 people to sacrifice their rights to personal liberty, privacy and bodily integrity.

5. Further, there is an established medical phenomenon known as viral or vaccine interference, meaning that one vaccine may increase the risk of infection, hospitalization, and death from another vaccine or another virus.

6. Based on observational studies, including one which specifically found that the flu vaccine was associated with a significantly increased risk of contracting common coronaviruses, it is possible that this flu vaccine mandate could cause increased COVID-19 cases, hospitalizations, and deaths – not the reverse.

[1] The Executive Order (hereinafter sometimes referred to as the "EO") is attached to this Complaint as Exhibit "A").

[2] As discussed *infra* at pages 7-8, the fear of a hospital bed shortage in California is contradicted by the data compiled by the California Department of Public Health ("CDPH").

7. It is unethical to force all UC community members to be injected with the flu vaccine until there are placebo controlled clinical trials that prove the flu vaccine will not cause increased COVID-19 cases, more hospitalizations and more deaths by way of vaccine interference.

8. Until those trials are completed, mandating the entire UC community to be vaccinated against the flu would turn them all into involuntary participants in a *de facto* large clinical trial that would answer these critical, but unanswered, questions.

9. Thus, in a literal sense, the EO is turning the UC community into human guinea pigs. Plaintiffs and many others in the UC community do not consent to participate in this *de facto* unethical, forced clinical trial.

10. The burden of proof is on the Defendants to prove to this Court that the flu vaccine can be safely administered without causing unnecessary harm during this pandemic. But that burden cannot be met because there are no such studies.

11. While the EO does offer a religious and disability accommodation (not an exemption) to UC employees, no such accommodations exist for UC students. Thus, the third reason the Court must void the EO is that it is discriminatory on its face and violates the students' Equal Protection and First Amendment rights. It also violates their civil rights under the California constitution, and two state civil rights statutes.

12. Only 43% of adult Californians consent to be vaccinated against the flu.[3] Thus, opposition to the flu vaccine is not a fringe position; it is the position of a clear majority of Californians.

13. There is no U.S. judicial precedent for a state-wide, adult, mandatory vaccination order in a time of pandemic, when the mandate is for a vaccine unrelated to the pandemic. The lack of precedent is understandable since there is no constitutionally acceptable justification to disregard

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[3]This is the number for the 2018-19 flu season which is up from prior years. United States Centers for Disease Control and Prevention (CDC) (2019), Flu Vaccination Coverage, United States, 2018–19 Influenza Season. *FluVaxView.* https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm

the personal liberty, privacy and bodily integrity rights of Plaintiffs and hundreds of thousands of members of the UC community living across the state in these circumstances.

14. The Plaintiffs herein for themselves and for the many other like-minded UC community members do not consent.

THE PARTIES

The Plaintiffs

15. All Plaintiffs in this case have received all the mandatory vaccines required as of the time they attended public school. The two student Plaintiffs are compliant with the current UC mandated vaccine schedule.

16. CINDY KIEL, JD is the Executive Associate Vice Chancellor of the Office of Research at the University of California, Davis. She provides leadership and counsel over research administration and compliance areas for the University. She has specific expertise and oversight on ethical and informed consent issues for clinical trials at the UC Davis campuses. Prior to her academic career, she was a practicing attorney working in fields including consumer protection and education law. Executive Associate Vice Chancellor Kiel opposes the EO requirement for mandatory flu vaccination.

17. MCKENNA HENDRICKS is a junior at UC Santa Barbara majoring in psychology. She is fully vaccine complaint with the UC rules for students (with the exception of the EO) and does not oppose vaccines. However, she does not want to take the flu vaccine. Her mother is a nurse and supports her decision.

18. EDGAR DE GRACIA is a senior at UCLA and hopes to go to law school next year. He is thirty five years old, received all his school required vaccinations (with the exception of the EO flu vaccine), but does not want to take the flu shot since he is extremely health conscious and is willing to take the risk of contracting the flu due to his excellent health.

19. LELAND VANDERPOEL is a Television Technician on the UCSF Fresno IT staff. Fresno is a satellite extension of the UCSF Medical Education Program. His specialty is videoconferencing technology. He opposes the EO's flu mandate.

The Defendants

20. MICHAEL V. DRAKE is the President of the University of California, as of August 1, 2020. President Drake and the University of California have a principal place of business in Alameda County.

21. THE REGENTS OF THE UNIVERSITY OF CALIFORNIA is a public legal entity charged with the government of a public trust which under Article IX, Section 9 of the state Constitution has been given "full powers of organization and government, subject only to such legislative control as may be necessary to insure compliance with the terms of the endowments of the university and the security of its funds." Its principal place of business and executive operations is in Alameda County.

JURISDICTION AND VENUE

22. This court has jurisdiction under the Declaratory Judgment Act, Cal. Code Civ. Proc. section 1060 *et seq.*, Cal. Civ. Code sections 525 and 526 on the injunction claim, Cal. Civ. Code section 51 *et seq.*, on the Unruh Civil Rights Act claim and Cal. Gov't Code section 11135 *et seq.*, the California Civil Rights Act, and 42 U.S.C. section 1983.

23. Venue is proper in this county as it is the principal place of business for both Defendants under Cal. Code Civ. Proc. section 395.

FACTUAL BACKGROUND

The Executive Order

24. On July 31, 2020, the last official day of her tenure, now former president Janet Napolitano signed an executive order requiring all 280,000 UC students and all 230,000 faculty and staff to receive a flu vaccine by November 1, 2020[4] (with certain accommodations discussed *infra*.).

[4] Upon information and belief, at least one UC athletic program (UCLA) has required compliance by October 1, 2020.

25. This Executive Order will likely lead to massive non-compliance, causing chaos and discontent in the UC community, unless the Court voids this Executive Order, or the University rescinds it.

The Stated Justification for The Executive Order Is Manifestly Unconnected to The Coronavirus Pandemic

26. The stated justification for mandating the flu vaccine for all 510,000 members of the UC community in the EO "Background and Findings" is that 1. there are a few described studies (less than ten),[5] which suggest that the flu vaccine reduces flu hospitalizations and the level of flu sickness in some groups like seniors and pregnant women, and 2. mandating a flu vaccine on the entire UC community might free up hospital beds if there were to be a hospital bed shortage during a second wave of the coronavirus pandemic.

27. However, the contention that there will be a shortage of hospital beds is not borne out by the facts. Here is the most recent CDPH data on hospital beds usage: Seasonal flu hospital admissions suggest that the peak rates were during the 2016–2017 and 2017–2018 influenza seasons (12.2 and 20.4 influenza hospitalizations per 100,000, respectively), which did not overburden hospitals.

28. Assuming worst case COVID-19 numbers (using data to date), California has not exceeded more than 10 hospitalizations per 100,000/week, since March 7th in any week of the pandemic through August 22nd.[6]

29. Where is the hospitalization crisis that UC claims to be helping avoid? According to Kaiser Permanente, there are about 180 hospital beds per 100,000 California residents.[7]

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[5] At least one part of the assertion that flu vaccination reduces hospitalizations is unproven if not proven to be untrue, but that is best left for the preliminary injunction part of this case.

[6] CDPH (2020). Influenza Surveillance Program. *Flu Reports.* https://www.cdph.ca.gov/Programs/CID/DCDC/pages/immunization/flu-reports.aspx; CDC (2020). Laboratory-Confirmed COVID-19-Associated Hospitalizations, Preliminary cumulative rates as of Aug 15, 2020. *Covid-Net*. https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

[7] Kaiser Family Foundation (2020). Hospital Beds per 1,000 Population by Ownership Type. *State Health Facts.* https://www.kff.org/other/state-indicator/beds-by-

30. Therefore, the EO's stated rationale of freeing up hospital beds in case there is an overload is factually inconsistent with CDPH's own data on hospital usage during flu seasons.

A Recent DOD Observational Study Suggests That the Flu Shot May Significantly Increase the Risk of Acquiring Some Kinds of Coronavirus (Though Not Necessarily COVID-19)

31. A Department of Defense observational study published in early January 2020, with the title: "Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017-2018 influenza season" is the only actual scientific evidence currently available about the relationship between the flu vaccine and coronavirus susceptibility.

32. The first words of the abstract are as follows:

"**Purpose**: Receiving the influenza vaccine may increase the risk of other respiratory viruses, a phenomenon known as virus interference." (emphasis in original text).[8] The study compared respiratory virus status among DOD personnel based on their influenza vaccination status.

33. According to the author, the study produced "mixed results." Here are the exact words used by the author in stating his conclusions:

"Conclusions: Receipt of influenza vaccination was not associated with virus interference among our population. Examining virus interference by specific respiratory viruses showed mixed results. **Vaccine derived virus interference was significantly associated with coronavirus and human metapneumovirus;** however, significant protection with vaccination was associated not only with most influenza viruses, but also parainfluenza, RSV, and non-influenza virus coinfections." [emphasis added] *Id.* (To some, the first sentence of the abstract's conclusion seems inconsistent with the highlighted text because the study in fact found a significant (36%) increase and association between the flu vaccine and the four studied coronavirus strains).[9]

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ownership/?currentTimeframe=0&selectedRows=%7B%22states%22:%7B%22california%22:%7B%7D%7D%7D&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D

[8] Wolff, G. (2020). Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017-2018 influenza season. *Vaccine*;38(2):350-354. doi: 10.1016/j.vaccine.2019.10.005

[9] This study was published in early January 2020, right before the pandemic came to the U.S. Recently, for unknown but perhaps obvious reasons, the study's author pointed out in a non-peer

34. In 2018, the CDC's "Assessment of temporally-related acute respiratory illness following influenza vaccination"10 studied virus interference. It specifically found there was an increase of acute respiratory infections caused by non-influenza respiratory pathogens following influenza vaccination compared to unvaccinated children during the same period. The authors recommended that potential mechanisms for this association warrant further investigation.[10]

35. While the study was limited to children, and thus cannot be directly extrapolated as applying to adults, (because of the differences in immune system development), it is another piece of the puzzle about whether the flu vaccine causes vaccine or virus interference with the pandemic coronavirus.

36. Do these two studies (and a few others that deal with vaccine interference from the flu vaccine causing upper respiratory infections) prove that taking the flu shot will cause or even increase the risk of contracting or dying from COVID? No, of course not. These are observational studies which establish associations but do not necessarily determine causation.

37. However, these studies should raise in any observant, unbiased scientist the index of suspicion that there might be a virus interference connection between the flu vaccine and the pandemic coronavirus.

38. Based on these studies, it seems clear that the EO *could* cause devastating harm to the UC community. And that should give anyone pause to think before taking the flu shot, at least if the UC community has the option to refuse, which it does not under the EO.

39. Arguably, this is the type of information routinely provided to clinical study participants so they can intelligently weigh the risks versus the benefits in participating in the study.

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reviewed Letter to the Editor that the virus interference results he found showing an increased (36%) risk and association between the flu vaccine and coronavirus might not apply to the pandemic coronavirus strain because it is "novel." He also suggested that his finding supports everyone getting vaccinated against the flu because of his other findings, presumably based on the author's hopes that the significant increase he found does not carry forward to COVID-19 because it is "novel." Wolff, G (2020). Letter to the Editor. *Vaccine*;38(30):4651. doi.org/10.1016/j.vaccine.2020.04.016.

[10] Rikin, S, et al. (2018). Assessment of temporally-related acute respiratory illness following influenza vaccination. *Vaccine*;36 (15):1958-1964. https://doi.org/10.1016/j.vaccine.2018.02.105.

40. But because this is a vaccine mandate, the UC community has no choice. Thus this important information arguably is not technically relevant in a forced vaccination scenario, (which might be the reason that this information has been omitted from the EO, and why it only includes studies showing the collateral benefit, at best, of the flu vaccine *in normal times*).

41. To the extent that public health experts demand proof of a flu vaccine's connection to COVID-19, they have it backwards. Given the existing evidence on vaccine or viral interference, Plaintiffs submit that the Defendants have the burden of proof to demonstrate that the flu vaccine will not cause vaccine interference, leading to increased COVID-19 infections, hospitalizations and deaths.

42. There is no such proof yet. Until there are fully controlled clinical studies, it is unethical under all existing US and worldwide human research ethical standards and guidelines to force anyone in the UC community to be injected with the flu vaccine during this COVID-19 pandemic on the factually disproven justification that the flu mandate is necessary to free up hospital beds based on the multiple "ifs."

43. Finally, although it may not be not necessary to go into the details of the safety and efficacy of the flu vaccine, some background and key points for context may be in order, because it underscores why Plaintiffs and many others think that a state-wide mandate for all UC personnel is unwise and could be harmful.

44. None of the flu vaccines that will be on the market for the 2020-2021 year have been tested against an inert placebo. Additionally, there is no research showing that this year's slate of flu vaccines will be effective against seasonal influenza in the upcoming year, because every year's flu strain(s) is/are different from past years. Manufacturers take their best guess as to what the strain will look like in the future. Every manufacturer's vaccine insert states that there is no guarantee that the product will actually work.

45. The CDC will not be able to ascertain if there is any protective effective until the influenza season concludes. Flu vaccinations have also not been evaluated in clinical trials for its mutagenicity, carcinogenicity or effects on reproductive systems.

46. There is no way to know whether the influenza vaccine program will actually prevent any cases of influenza in the upcoming flu season or if it does, at what level of effectiveness.

47. If history is an indicator, it is more likely than not that it will be less than 50% effective against the flu strains it purports to provide protection against thus, rendering the UC system's stated purpose of reducing strain on the health system less persuasive.

48. The UC campuses already plan on routine monitoring, asymptomatic testing of students, faculty, and staff in addition to symptomatic testing. This surveillance and testing will continue at the same level regardless of the level of respiratory symptoms presenting in the population and if an individual with flu-like symptoms tests negative for SARSCOV2, then the contact tracing mechanisms would not be engaged.

49. The UC's concern that individuals presenting with flu-like symptoms during the upcoming winter will overlap with COVID19 symptoms thus increasing the burden on the system's coronavirus surveillance, testing and tracking mechanisms is a flawed argument and speculative.

50. In terms of the vaccine's risk profile, the flu vaccine manufacturers admit that their product is or may be associated with a risk of serious harm. The popular flu vaccine Flulaval's package insert lists the adverse effects associated with it found in both pre-marketing studies and post-marketing reports and include many local and systemic adverse effects, as well as serious adverse effects.[11] Other flu vaccine package inserts include similar lengthy lists of adverse effects associated with the vaccine. **HOWEVER, there is no such warning in the EO.**

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[11] https://www.fda.gov/media/74537/download (Exhibit "B" attached) according to which:

> "In adults who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (60%); the most common (≥10%) solicited systemic adverse reactions were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%)...Trial 1 (NCT01196975) was a randomized, double-blind, active-controlled, safety and immunogenicity trial.... The unsolicited adverse reactions that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included nasopharyngitis, upper respiratory tract infection, headache, cough, and oropharyngeal pain. Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively....Beyond those events reported in the clinical trials for FLULAVAL QUADRIVALENT or FLULAVAL, the following adverse reactions have been identified during post approval use of FLULAVAL QUADRIVALENT or FLULAVAL (trivalent influenza vaccine): ... Blood and Lymphatic System Disorders Lymphadenopathy; Eye

51. The risks associated with the administration of the flu vaccine are critical to the Court's decision in this case, and specifically in the balancing of these serious documented risks against the stated need for the flu mandate, namely the asserted but speculative, debunked, collateral advantage of freeing up hospital beds. For that reason, a copy of Flulaval's entire package insert is attached.(Exhibit "B"). It is a sobering document to read, especially for the 510,000 UC member community who are being forced to take it. The Court is encouraged to carefully consider it in deciding the safety, wisdom, and constitutionality of the EO's mandate.

52. On the legal side, as discussed more fully in the Second Cause of Action, there is no precedent in any US court to allow this kind of broad adult, state-wide mandate for a vaccine unrelated to a pandemic and based on such a collateral, speculative, and factually-debunked "free up the hospital beds" justification.

53. This Court should not allow the EO to go into effect for the reasons set forth in the following causes of action, and in particular based on Plaintiffs' and the rest of the UC community members' rights to privacy and bodily integrity enshrined in and secured by the U.S. and California Constitutions.

Disorders; Eye pain, photophobia; Gastrointestinal Disorders; Dysphagia, vomiting; General Disorders and Administration Site Conditions; Chest pain, injection site inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess; Immune System Disorders; Allergic reactions including anaphylaxis, angioedema; Infections and Infestations; Rhinitis, laryngitis, cellulitis; Musculoskeletal and Connective Tissue Disorders Muscle weakness, arthritis; Nervous System Disorders; Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis; Psychiatric Disorders; Insomnia; Respiratory, Thoracic, and Mediastinal Disorders Dyspnea, dysphonia, bronchospasm, throat tightness; Skin and Subcutaneous Tissue Disorders; Urticaria, localized or generalized rash, pruritus, sweating. Vascular Disorders; Flushing, pallor." GlaxoSmithKline (2020). FLULAVAL QUADRIVALENT (Influenza Vaccine).

FIRST CAUSE OF ACTION

DECLARATORY JUDGMENT ON BEHALF OF ALL PLAINTIFFS AND AGAINST BOTH DEFENDANTS THAT THE EXECUTIVE ORDER WAS AN *ULTRA VIRES* ACT BEYOND THE AUTHORITY GIVEN TO THE UC FORMER PRESIDENT AND IS NULL AND VOID CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.* [12]

54. Plaintiffs repeat and reallege the allegations set forth above.

55. There is nothing in the text of the EO which states or implies that the former president consulted with or received any formal input from the Regents, the University's faculty Senate, or the any of the unions representing 79,000 UC employees before she issued it.

56. Rather, the stated authority for issuing the EO is "the authority vested in me by Bylaw, 30, Bylaw 22.1, Regents Policy 1500 and Standing Order 100.4(ee) . . . ." (EO at page 2, Exhibit "A" attached). However, none of these documents justify the unilateral action taken by the former president.

57. **If fact, the very governance documents referenced in the EO prove that the president improperly issued it.**

58. Bylaw 30 provides, *inter alia,* that the president is "expected to consult with the Academic Senate, consistent with the principles of shared governance, on **issues of significance to the general welfare and conduct of the faculty**." (emphasis added) Compelled vaccination, which (1) is not directly related to the pandemic, (2) has resulted in the payment of almost $1 billion in federal compensation,[13] (3) has been shown to increase the risk of harm from some coronaviruses, (4) has been demonstrated to be ineffective in over half of its recipients, and (5) can actually spread the flu -- is surely an issue of significance to the general welfare and conduct of the faculty.

59. Bylaw 22.1 grants the full powers, organization and government of the University to the Regents and delegates to the President the power to oversee the operation of the University in accordance with adopted policies and directives **"and as further specified by Bylaw 30,"** subject to the Board (emphasis added). Contrary to the EO's claim of authority under Bylaw 22.1, this Bylaw

[12] All subsequent causes of action are also against both Defendants.

[13] United States Health & Human Services (2020). Vaccine Injury Compensation Data. *HRSA.* https://www.hrsa.gov/vaccine-compensation/data/index.html

does grant the president the authority to issue the EO. Rather, by incorporating Bylaw 30 and its limitation of the president's power and the obligation to consult the faculty, Bylaw 30 further demonstrates that the former president's EO is *ultra vires* and inconsistent with her governing obligations and limitations.

60. Without more and regardless of the content of the other referenced sources or bases of the EO, the former president's failure to comply with the Bylaws and consult with the Academic Senate means that the EO is in violation of the Bylaws and *ipso facto ultra vires*, which justifies the declaratory relief requested in this cause of action.

61. The former president's failure to comply with the Bylaws, to consult the faculty before issuing the EO, and to so note such consultation in the EO is a breach of the shared governance norms deeply embedded in the UC community.

62. Regents Policy Statement 1500 provides additional governance authority that the action was *ultra vires*, as it provides that "The President is expected to direct the management and administration of the University of California System consistent with the Bylaws . . . ." Her actions violate Bylaw 30 as indicated above.

63. Requiring all 510,000 members of the UC community to get a vaccine against a disease not causing the pandemic and for an at best collateral, debunked benefit is without legal precedent in this country.

64. Common sense and common decency also require that the Regents should have been consulted and some Regents-approved process undertaken before the former president took such an extreme measure.

65. Standing Order 100.4 (ee) sets out several dozen specific things the president is permitted to do, like to award degrees, hire and fire staff and set compensation, modify budget estimates and many very specific tasks. This Standing Order does not appear to permit a president to mandate a flu vaccine during a coronavirus pandemic.

66. Based on the foregoing, none of the governance authority documents cited in the EO provide a basis for the former president's ordering the 510,000 UC community members to be

subjected to compulsory flu vaccination on pain of being terminated or unable to attend class. Thus, the former president issued the EO without proper authority. It is *ultra vires* and should be declared null and void by this Court.[14]

SECOND CAUSE OF ACTION

THE EO VIOLATES THE FEDERAL CONSTITUTIONAL PRIVACY RIGHTS OF ALL PLAINTIFFS 42 USC SECTION 1983 AND DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*

67. Plaintiffs repeat and reallege the allegations set forth above.

68. Each Plaintiff has an undeniable right of privacy, which includes the right to control his or her own body. The United States Supreme Court has consistently recognized the constitutional right of every non-incarcerated individual to remain free from forced medical treatment, even life-saving treatment. *See e.g., Cruzan v. Director, Missouri Dept of Health,* 497 US 261, 279 (1990) ("It cannot be disputed that the Due Process Clause protects an interest in life as well as an interest in refusing life-sustaining medical treatment.")

69. Of course, since the landmark 1905 decision in *Jacobson v. Massachusetts,* 197 U.S. 11 (1905), state and local governments under their police powers have a right to protect the public, including in proper circumstances and subject to judicial scrutiny, issue vaccine mandates.

70. The mandate affirmed in *Jacobson* was for the smallpox vaccination during a smallpox epidemic. But it was not an absolute or true mandate since the penalty for non-compliance was a $5.00 fine ($140 in today's money).

71. More importantly, *Jacobson* stands for the proposition that public health regulations require five elements to be constitutional: (1) public health necessity, (2) reasonable means, (3)

[14] Even if the former president somehow did have the authority under the governance documents, the Court should still overturn the EO because vaccination is an issue of statewide concern, and the EO is more restrictive than state statutes that regulate this area. Meaning, since there is no compulsory flu vaccination for the other 39.5 million Californians , the EO is a very significant intrusion in the academic arena and should be struck down under *Scharf v. Regents of The University of California* (1991) 234 Cal.App.3d 1393, 1402-1404 and the cases cited therein.

proportionality, (4) harm avoidance, and (5) non-discrimination. The executive order issued by the former president meets none of these required elements as will be demonstrated at the trial and in the preliminary injunction motion.

72. Later courts, including the U.S. Supreme Court, have affirmed certain k-12 school vaccine mandates as a condition of school attendance, subject to specified exemptions. And there have been mandates for various flu vaccines for health practitioners. However, at least one court has issued a temporary restraining order against a state-mandated swine flu vaccine mandate for healthcare workers during the swine flu epidemic, but even in that case where the mandate was rejected, there was a direct asserted benefit between the shot and the epidemic. [15]

73. Still, no court has ever upheld a general mandatory vaccination order for adults for a vaccine that does not immunize them against the outbreak, epidemic or pandemic that is the cause and source of the immediate public health crisis. Imagine during the Spanish flu pandemic, some government entity wanted to force people to take smallpox or yellow fever vaccines on the rationale that if people get sick from those diseases, they would take hospital beds away from Spanish flu patients. It is hard to imagine that would have been accepted by the courts.

74. The EO mandates a vaccine that has **no** proven benefit against the virus causing the pandemic. The EO is not based on evidence-based medicine. It is based on public policy by simile and wishful thinking, and an absurdly speculative collateral benefit, not borne out by actual hospitalization data. (page 6, para. 27 to page 7 para. 30 *supra*). That is a far cry from what faced the courts in *Jacobson* and its progeny.

75. Plaintiffs can find no case in the history of US jurisprudence that has ever upheld forcing a large group of adults over an entire state to take one vaccine because there is an unrelated

[15] The TRO in that case is unavailable to the Plaintiffs currently. Here is an article describing the order and the surrounding legal and ethical issues. Lowenberg, K (2009). Update on New York Mandatory H1N1 Vaccinations. *Stanford Law and Biosciences Blog.* https://law.stanford.edu/2009/10/22/update-on-new-york-mandatory-h1n1-vaccinations/. See also the *New York Times* article, which relates "the litigation in Albany and a parallel case in New York City reflect an undercurrent of public anxiety about the swine flu vaccine in particular because of the close attention it has received, despite the assurances of state and federal health officials that it is as safe as any other vaccine." Hartocollis, A, *et al.* (2009). Albany Judge Blocks Vaccination Rule. *NY Times.* https://archive.nytimes.com/www.nytimes.com/2009/10/17/nyregion/17vaccine.html

epidemic, based on some speculated collateral benefit. There never should be one because it is a constitutionally farfetched proposition that violates the fundamental right to bodily integrity and control without any proven countervailing benefit to the society. Given the potential risk of the flu vaccine suggested by vaccine or vires interference, unconstitutionality of the EO flu mandate seems ever clearer.

76. Because these are constitutional violations, harm is presumed, and specific injury to a plaintiff need not be demonstrated in this or any other cause of action asserting a federal constitutional violation. And yet due to the EO, Plaintiffs have suffered, are suffering, and/or imminently will suffer harm as herein alleged.

77. The short of it is that since the flu shot bears no direct relationship or proven benefit to COVID-19, it is unconstitutional for any government, including a university, to force anyone to take it because of some collateral future possible benefit. The right to personal freedom and bodily integrity demands this result.

78. Accordingly, the Court should declare the EO a violation of the right to privacy under the Fifth and Fourteenth Amendments' guaranties of bodily integrity and declare that the EO is null and void.

THIRD CAUSE OF ACTION

THE EO VIOLATES ALL PLAINTIFFS' STATE CONSTITUTIONALLY PROTECTED RIGHTS TO PRIVACY AND BODILY INTEGRITY DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*

79. Plaintiffs repeat and reallege the allegations set forth above.

80. In 1974, an amendment to the California Constitution elevated the right of privacy to an "inalienable right." Cal. Const. art. I, § 1, *Lantz v. Superior Court* (1994) 28 Cal. App. 4th 1839, 1848. *See also*, California Constitution, Article I, section 7, especially "A person may not be deprived of life, liberty, or property without due process of law or denied equal protection of the laws" and "maximizing the educational opportunities and protecting the health and safety of all public school pupils".

81. The California courts recognize the "relatively certain principle that a competent adult has the right to refuse medical treatment, even treatment necessary to sustain life." *Conservatorship of Wendland* (2001) 26 Cal.4th 519, 530; see also *Riese v. St. Mary's Hospital & Medical Center* (1987) 209 Cal.App.3d 1303, 1317.

82. As explained by *Wendland, supra,* 26 Cal.4th at pp. 531-532, this right is grounded in both state constitutional and common law, together with the right of privacy guaranteed by the California Constitution, article I, section 1 "guarantee[ing] to the individual the freedom to choose to reject, or refuse to consent to, intrusions of his bodily integrity." [16]

83. When balancing privacy rights against public health rights, the Court should come down in favor of privacy in this case for the simple reason that there is no proven benefit that a flu vaccine can prevent or mitigate the effects of any coronavirus, and there is evidence it may increase the risk of harm to coronavirus patients and cause harm to many in the UC community.

84. For these reasons, the Court should declare that the EO violates Plaintiffs' privacy rights and rights of bodily integrity conferred by the California Constitution and declare the EO null and void.

[16] Notably though, the California Supreme Court qualified the right to refuse medical treatment, albeit in dicta, in the case of *Thor v. Superior Court* (1993) 5 Cal. 4th 725, 738: "Having reached this conclusion, we nevertheless recognize that, while fundamentally compelling, the right to be free from nonconsensual invasions of bodily integrity is not absolute. Four state interests generally identify the countervailing considerations in determining the scope of patient autonomy: preserving life, preventing suicide, maintaining the integrity of the medical profession, and protecting innocent third parties. [citations omitted]"

FOURTH CAUSE OF ACTION

DECLARATORY JUDGMENT THAT THE EO VIOLATES THE FOURTEENTH AMENDMENT'S EQUAL PROTECTION RIGHTS OF THE STUDENT PLAINTIFFS HENDRICKS AND DE GRACIA 42 USC SECTION 1983 and DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*

85. Plaintiffs repeat and reallege the allegations set forth above.

86. The University of California is a state-created, state-financed and state-run public trust education system, and as such, it is subject to the Fifth Amendment right to equal protection of the law through the Fourteenth Amendment.

87. The EO provides that university employees may seek a "religious accommodation" to the flu vaccine to be "adjudicated through the interactive process consistent with existing location policies and procedures (EO at page 2 paragraph 1 c to page 3).

88. There is no similar religious accommodation for the university students, which violates Plaintiff students' rights to the equal protection of the law and First Amendment protected religious rights, which must be governed by strict scrutiny because they are fundamental rights. Harm is both actual and imminent for Plaintiffs. It is also presumed by law for such constitutional violations, and without more, the Court should enter a declaratory judgment that the EO violates the UC student Plaintiffs' constitutional rights and declare the EO null and void.

FIFTH CAUSE OF ACTION

DECLARATORY JUDGMENT THAT THE EO VIOLATES THE UNRUH CIVIL RIGHTS ACT OF THE RIGHTS OF UC STUDENT PLAINTIFFS HENDRICKS AND DE GRACIA, DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*

89. Plaintiffs repeat and reallege the allegations set forth above.

90. California Civil Code Section 51 (the Unruh Civil Rights Act per b) provides:

> *All persons within the jurisdiction of this state are free and equal, and no matter what their* ***sex, race, color, religion,*** *ancestry, national origin, disability, medical condition, genetic information, marital status, sexual orientation, citizenship, primary language, or immigration status are* ***entitled to the full and equal accommodations,*** *advantages, facilities, privileges, or services* ***in all business establishments of every kind*** *whatsoever.* (Emphasis added).

91. The UC System is a business establishment within the meaning of Cal. Civ. Code section 51, *et seq*. within the jurisdiction of this filing Court. Defendant UC is one of the largest employers in the State of California, receiving approximately $1.7B annually in revenue from Auxiliary Businesses (campus services that charge fees for goods and services and therefore are self-supporting. Examples include housing, meals and bookstores).

92. “Religion” includes all aspects of religious belief, observance, and practice. Cal Civ. Code section 51e(3).

93. "Sex" includes, but is not limited to, pregnancy. Cal. Civ. Code section 51e(5).

94. The EO grants employees the right to seek a religious accommodation to the flu vaccine requirement but makes no such accommodation to the UC’s 280,000 students.

95. The EO discriminates against students who become, and those who are aware, and even possibly unaware, that they are pregnant and in greater danger of injury from a mandatory vaccine since there is no pregnancy exemption in Defendant's EO.

96. The EO violates the Unruh Civil Rights Act and must be enjoined from being permitted to take effect. Because of the EO’s policy, disparate treatment allows some to have been denied full and equal access to UC while others are not. These violations are ongoing. Defendant's failure and refusal to correct constitutes intentional discrimination.

97. Employees and students who do not comply will not be permitted to set foot on campus on November 1, 2020.

98. Defendants’ actions were and are in violation of the Unruh Act.

99. Plaintiffs are also entitled to statutory damages under Cal. Civ. Code section 52.

100. Cal. Civ. Code section 52 further entitles Plaintiffs to reasonable attorneys' fees and costs.

SIXTH CAUSE OF ACTION

GOVERNMENT CODE 11135 ESTABLISHED CIVIL RIGHTS ON BEHALF OF UC STUDENT PLAINTIFFS HENDRICKS AND DE GRACIA DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*

101. Plaintiffs repeat and reallege the allegations set forth above.

102. California Government Code section 11135, enacted in 1977, is California's civil rights analogue to Title VI of the Federal Civil Rights Act. Section 11135(a) states that:

> *No person in the State of California shall, on the basis of* ***sex,*** *race, color,* ***religion,*** *ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, or sexual orientation,* ***be unlawfully denied full and equal access to the benefits*** *of, or be unlawfully subjected to discrimination under, any program or activity that is conducted, operated, or administered by the state or by any state agency, is funded directly* ***by the state, or receives any financial assistance from the state.*** *Notwithstanding Section 11000, this section applies to the California State University.* Cal. Gov. Code section 11135(a) (emphasis added)

103. Defendant UC receives financial assistance from the State of California sufficient to invoke the coverage of Government Code section 11135 *et seq.* The UC System receives approximately $6.46 billion in Contracts and Grants, which include federal, state, local and private grants annually.

104. Since 2016, UC has a pattern and practice of not recognizing a student's religious belief (incorporated in the pre-SB 277 personal belief exemption) against mandatory vaccination, thereby creating conditions that have a discriminatory impact on plaintiffs and the public based on religion. This is a violation of Plaintiffs' civil rights.

105. Defendants' unlawful, discriminatory practice creates or establishes operating methods and conditions that have the purpose or effect of denying them the benefits of, or otherwise subjecting Plaintiffs to, discrimination.

106. Defendants' pattern and practice result in repeated violations of the anti-discrimination mandates under California Government Code section 11135 and violates the Plaintiffs' rights to full and equal protection under the law.

107. For all the reasons described above, Defendants have violated and continue to violate California Government Code section 11135(b).

108. Gov. Code section 11139 provides a private right of action to enforce section 11135, stating: "This article and regulations adopted pursuant to this article may be enforced by a civil action for equitable relief, which shall be independent of any other rights and remedies."

109. Defendants have refused to provide Plaintiffs with full and equal access to their facilities, programs, services, and activities as required by California Government Code section 11135 *et seq.*

110. Because Defendants' discriminatory conduct is ongoing, declaratory and injunctive relief are appropriate remedies.

111. Plaintiffs also are entitled to reasonable attorneys' fees and costs incurred in bringing this action pursuant to the rights, procedures, and remedies set forth under in California Government Code sections 11135 and 11139.

SEVENTH CAUSE OF ACTION

VIOLATION OF THE PUBLIC TRUST DOCTRINE UNDER THE 5TH AND 14TH AMENDMENTS ASSERTED ON BEHALF OF THE UC EMPLOYEE PLAINTIFFS DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*, AND 42 USC SECTION 1983

112. Plaintiffs repeat and reallege the allegations set forth above.

113. The University of California is a Public Trust established under the authority of the CA Constitution art IX § 9 (2018) California Constitution Article IX (in pertinent part) "*The University of California shall constitute a public trust, and its organization and government shall be perpetually continued in the form and character . . .*"

114. The EO states: (in relevant part): *"*Employees. Effective November 1, 2020, no person employed by the University or working on-site at any location owned, operated, or otherwise controlled by the University may report to that site for work unless they have received the 2020-2021 flu vaccine or an approved medical exemption."

115. 42 U.S.C. section 1983 creates a cause of action and is the vehicle whereby plaintiffs can challenge actions by governmental officials acting under color of state law that deprives another of rights guaranteed under the Constitution applicable to state law as evidenced by CACI 3000.

116. Plaintiffs, as employees, students, and staff, are beneficiaries of rights under the public trust doctrine as guaranteed under the Fifth and Fourteenth Amendments to the Federal Constitution. Defendants are public employees and have a number of qualitatively different protectable interests of procedural due process. Before a public employer fires a public employee, the employees are entitled to due process.

117. Defendant Michael V. Drake, while purporting to perform official duties under color of authority, intentionally violates Plaintiffs' constitutional rights by mandating injection of a vaccine *which has no direct effect on the source of the current pandemic* as a condition of employment. Defendants' conduct violates Plaintiffs' rights to bodily autonomy under the 4th and 5th Amendment.

118. Plaintiffs will be harmed and Defendants' actions are a substantial factor in causing that harm. People have the right to make up their own minds whether they should take a flu shot to protect themselves, especially as there is no authoritative evidence that the flu vaccine will prevent or mitigate coronavirus, and there is evidence that the flu vaccine actually may increase the risk and create a danger in a coronavirus pandemic.

119. Defendants' EO will result in an unlawful Constructive Discharge by forcing Plaintiffs to resign, as they are not allowed to "report for work", thereby violating public policy and substantive due process. The choice of being force-injected or losing one's job is intolerable. It is coercion. Plaintiffs should not be summarily fired or disallowed to show up for work over this violation of bodily integrity.

120. If Plaintiffs were injured, disabled, or killed after receiving mandated flu shots, they would have zero recourse against the manufacturer for design defects or the University system because of the broad immunities granted to manufacturers and healthcare providers. *See e.g., Bruesewitz v. Wyeth*, 562 U.S. 223 (2011); California Health & Safety Code section 120455 ("No person shall be liable for any injury caused by an act or omission in the administration of a vaccine...")

121. As trustee, Defendant Regents has a duty to refrain from "substantial impairment" of these rights. Defendants' Executive Order has unconstitutionally caused, and continues to cause, a violation of a public trust. As a trustee, the affirmative aggregate acts of Defendant are unconstitutional and in contravention of the duty to be a steward of the trust. Defendant Regents has failed in the duty of care to safeguard the interests of Plaintiffs.

EIGHTH CAUSE OF ACTION

DECLARATORY JUDGEMENT ON BEHALF OF ALL PLAINTIFFS THAT THE EO IS ARBITRARY AND CAPRICIOUS AND AN ABUSE OF DISCRETION BY THE UC FORMER PRESIDENT AND HENCE IS NULL AND VOID DECLARATORY RELIEF, CAL. CODE CIV. PROC. SECTION 1060 *ET SEQ.*

122. Plaintiffs repeat and reallege the allegations set forth above.

123. Assuming *arguendo* that the Court determines that the former president had the authority to issue the EO, it should strike it down under the arbitrary and capricious standard based on the facts set forth hereinbefore.

NINTH CAUSE OF ACTION

INJUNCTIVE RELIEF, CODE OF CIV. PRO SECTION 526 (4) ON BEHALF OF ALL PLAINTIFFS

124. Plaintiffs repeat and reallege the allegations set forth above.

125. The balancing this Court must do is far different from the analysis that Courts have previously performed in vaccine mandate cases from *Jacobson* onwards. Because the mandate here is utterly speculative and foreign to the nature of the harm, because it is for something which has no proven benefit against the current pandemic, this case requires a different result from earlier cases.

126. There is no adequate remedy at law nor any pecuniary compensation that could adequately compensate Plaintiffs for the constitutional violations they would suffer if this mandate stands. In particular, the assaults on their privacy, bodily integrity and right to refuse unwanted medical intervention require injunctive relief. Thus, this relief is warranted under Code of Civ. Proc. section 526 (4).

PRAYER FOR RELIEF

For the foregoing reasons, after the trial of this action, Plaintiffs respectfully request that judgment be entered against both defendants,

A. That the Court enter a declaratory judgement voiding the Executive Order issued by Former UC President Janet Napolitano requiring the entire UC community to be subjected to the flu vaccine as set forth in the First through Eighth Causes of Action,

B. A permanent injunction enjoining the Defendants from enforcing the Executive Order, as set out in the Ninth Cause of Action,

C. Together with costs, reasonable attorneys' fees provided under the relevant statutes as set forth above, and such other and further relief as the court deems just and proper.

DATED: August 27, 2020

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EXHIBIT “A”

University of California
Executive Order
July 31, 2020

Background and Findings

As of this date, the world is facing a severe health crisis in which COVID-19, a new respiratory illness caused by a novel coronavirus, places millions of people at risk of serious illness or death. The World Health Organization has declared that the disease is a pandemic. Declarations of Emergency have been issued by the President of the United States, the Governor of California, and California counties and other local jurisdictions, including those where the University maintains campuses and other significant operations.

In California alone, notwithstanding concerted statewide efforts to mitigate the spread of the disease, nearly 400,000 people already have been diagnosed with COVID-19 and more than 7,500 have perished. As of this writing, statewide positivity rates and hospitalizations are trending upward; on any given day, over 8,000 are hospitalized and more than 2,000 are so sick that they are being treated in intensive care units.

On March 19 of this year, the State Public Health Officer issued an order directing all individuals living in the State to stay at home except as needed to facilitate authorized, necessary activities or to maintain the continuity of operations of critical infrastructure sectors. This order caused virtually every government agency and private organization in the State to transition to remote operations to the greatest extent possible. Since then, the State has developed and refined a Pandemic Roadmap to guide prudent resumption of on-site or in-person operations and the University is developing and implementing plans to transition remote activities back to its campuses consistent with applicable public health orders and directives.

According to the Centers for Disease Control & Prevention, flu vaccination has long been accepted as a safe and effective way to prevent millions of illnesses and thousands of related doctor and hospital visits every year. In recent years, flu vaccines have reduced the risk of flu-associated hospitalizations among older adults on average by about 40%. A 2018 study showed that from 2012 to 2015, flu vaccination among adults reduced the risk of being admitted to an intensive care unit (ICU) with flu by 82 percent. Flu vaccination has been associated with lower rates of some cardiac events among people with heart disease, especially among those who had had a cardiac event in the past year. It can reduce worsening and hospitalization for flu-related chronic lung disease. It has been shown in separate studies to be associated with reduced hospitalizations among people with diabetes and chronic lung disease. A 2018 study that included influenza seasons from 2010-2016 showed that getting a flu shot reduced a pregnant woman's risk of being hospitalized with flu by an average of 40 percent. Flu vaccination has been shown in several studies to reduce severity of illness in people who get vaccinated but still

get sick. For example, a 2017 study showed that flu vaccination reduced deaths, intensive care unit (ICU) admissions, ICU length of stay, and overall duration of hospitalization among hospitalized flu patients. A 2018 study showed that among adults hospitalized with flu, vaccinated patients were 59 percent less likely to be admitted to the ICU than those who had not been vaccinated. Among adults in the ICU with flu, vaccinated patients on average spent 4 fewer days in the hospital than those who were not vaccinated. Finally, by getting vaccinated, a person can protect those around them, including those who are more vulnerable to serious flu illness.

During the SARS-CoV-2 pandemic, where COVID-19, like influenza, results in respiratory symptoms, it is even more critical than usual to assure widespread vaccination. As California progresses through its roadmap, the possibility of an outbreak or surge that overwhelms the health care system and causes hospitals to adopt crisis standards of care necessarily increases – as of July 20, 2020, thousands of new cases are being reported every day and hospitals are experiencing shortages of testing supplies and medications necessary to treat COVID-19. Population-level interventions that decrease the likelihood of disease transmission, hospitalization, and ICU utilization must therefore be considered and adopted where feasible.

As President of the University, I have concluded that critical steps must be taken to reduce the likelihood of severe disease among students, faculty and staff, particularly those on campus, and in turn to reduce the likelihood that our health systems will be overwhelmed.

Executive Order

WHEREFORE AS PRESIDENT OF THE UNIVERSITY OF CALIFORNIA I DECLARE:

On the authority vested in me by Bylaw 30, Bylaw 22.1, Regents Policy 1500 and Standing Order 100.4(ee), and based on the foregoing circumstances, I hereby issue the following order, to be effective through the 2020-2021 flu season, and direct the following:

1. Each campus shall strongly encourage universal vaccination for all students, faculty, staff, and their families by October 31, 2020. Subject only to the exemptions and processes described below or in Attachment A:

    a. Deadline. Effective November 1, 2020, all students, faculty, and staff living, learning, or working at any UC location must receive a flu vaccine.

    b. Students. The Immunization Policy is hereby amended to add influenza vaccine to the list of required vaccines for the duration of a statewide or any local public health emergency declared in response to the SARS-CoV-2 pandemic. Student exemption requests shall be adjudicated consistent with the Immunization Exemption Policy.

    c. Employees. Effective November 1, 2020, no person employed by the University or working on-site at any location owned, operated, or otherwise controlled by the University may report to that site for work unless they have received the 2020-2021 flu vaccine or an approved medical exemption. Requests for disability or

religious accommodations will be adjudicated through the interactive process consistent with existing location policies and procedures.

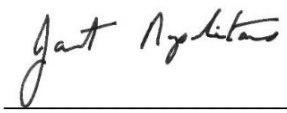
2. The University's health plans provide coverage for routine health maintenance vaccinations, including seasonal influenza vaccine, without copays to any covered students, faculty, staff, or their covered families.

3. The Vice President for Human Resources or her designee shall ensure that any applicable collective bargaining requirements are met with respect to the implementation of this order.

4. The Provost and the Executive Vice President or their designee(s) shall immediately consult with the Academic Senate on implementation of this order with respect to members of the University's faculty.

5. The Executive Vice President for UC Health or her designee shall provide technical guidance to the campuses at their request to facilitate execution of this mandate.

All University policies contrary to the provisions of this Executive Order, except those adopted by the Regents, shall be suspended to the extent of any conflict, during the period of this Order. The Executive Vice President – UC Health shall have the authority to issue further guidance about the parameters and use of this mandate, in consultation with the Provost and the Interim Vice President – Systemwide Human Resources.



Janet A. Napolitano
President

ATTACHMENT A: EMPLOYEE EXEMPTIONS

Medical Exemptions

A list of established medical contraindications to and precautions for flu vaccine can be found at the Centers for Disease Control and Prevention website, *Guide to Contraindications*, online at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html (scroll to IIV) and currently includes:

Contraindications:	Severe allergic reaction (e.g., anaphylaxis) after previous dose of influenza vaccine or to vaccine component.
Precautions:	Guillain-Barré Syndrome <6 weeks after a prior dose of influenza vaccine
	Moderate or severe acute illness with or without fever
	Egg allergy other than hives, e.g., angioedema, respiratory distress, lightheadedness, recurrent emesis; or required epinephrine or another emergency medical intervention (IIV may be administered in an inpatient or outpatient medical setting and under the supervision of a health care provider who is able to recognize and manage severe allergic conditions).

Any request for medical exemption must be documented on the attached Medical Exemption Request Form and submitted by an employee to the designated campus medical official (collectively an "Authorized HCP").

Faculty and Staff Appeals[1]

Each campus shall designate a local Immunization Exemption Appeals Officer (IEAO) for faculty and staff appeals. The IEAO shall have appropriate qualifications and training to adjudicate appeals, meaning at a minimum California licensure as a physician, physician's assistant, or advance practice nurse, who in turn may consult with other experts as necessary (e.g., environmental health and safety, infectious disease, occupational health).

Individuals who wish to appeal denial of a medical exemption must submit a written request to the Authorized HCP, along with documentation provided by their treating medical provider on the Medical Exemption Request Form.

Appeals should be de-identified and forwarded to the IEAO. Decisions should be communicated to the Authorized HCP, who will, in turn, communicate the IEAO decision to the faculty or staff member. IEAO decisions shall be rendered within 60 days of receipt by the IEAO and an

[1] An Immunization Exemption Appeals Committee (IEAC) has been established to evaluate student appeals. The IEAC is chaired by the UC Health Chief Medical Officer of Student Health and Counseling, and is convened as needed to evaluate medical exemption requests denied at the campus level for which students have submitted an appeal.

individual will not be barred from any campus activity while an appeal is pending. If the exemption denial is upheld, the faculty or staff member will be expected to comply with the immunization requirement within 15 days.

In active infectious disease outbreak situations, individuals granted medical exemptions may not be allowed to come to campus. These situations will be determined on a case-by-case basis, and in consultation with public health officials with jurisdiction.

The UC Immunization Exemption Policy Committee (IEPC) is a system-wide committee, appointed by the Executive Vice President, UC Health. It is comprised of UC faculty, staff and students, and public health officials. Members are selected from diverse backgrounds, and include actively practicing physicians, including at least one infectious disease specialist, and may also include faculty with expertise in a variety of other fields, such as medical ethics, law, public health, and international student services. Members serve a term of no less than one year. Campuses may consult with the IEPC on significant questions of policy.

University of California Medical Exemption Request Form

BERKELEY * DAVIS * IRVINE * LOS ANGELES * MERCED * RIVERSIDE * SAN DIEGO * SAN FRANCISCO * SANTA BARBARA * SANTA CRUZ

Name of Patient: _____

Status: ☐ Faculty ☐ Staff

Date of Birth: _____ MRN: _____

Name of Health Care Provider: _____

License Number: _____ Expiration Date: _____

State of Issuance: _____

License Type: ☐ Medical or Osteopathic Physician ☐ Nurse Practitioner ☐ Physician's Assistant

Practice Address: _____

Email: _____ Phone: _____

I hereby certify that the above-referenced patient qualifies for a medical exemption from influenza vaccine, as further provided below:

Reason for Exemption:

☐ CDC Contraindication ☐ CDC Precaution ☐ Manufacturer's Insert Contraindication ☐ Other

Provide a detailed explanation here regardless of the reason indicated immediately above:

_____

This contraindication or precaution is: ☐ Permanent ☐ Temporary

- If temporary, the expiration date for the exemption is: _____

Signature of Health Care Provider: _____

Date of Signature: _____

Faculty and Staff: Return this completed form to your campus-Authorized HCP.

For Official Use Only:

☐ Approved ☐ Denied Date: _____

Name: _____ Title: _____

Signature: _____

UC Location: <Choose One>

EXHIBIT “B”

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FLULAVAL safely and effectively. See full prescribing information for FLULAVAL.

FLULAVAL (Influenza Vaccine)
Suspension for Intramuscular Injection
20XX-20XX Formula
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	11/2016
Dosage and Administration (2.1, 2.2)	11/2016

---------- INDICATIONS AND USAGE----------

FLULAVAL is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FLULAVAL is approved for use in persons aged 6 months and older. (1)

----------DOSAGE AND ADMINISTRATION----------

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
6 months through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart (2.1)
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each) (2.1)
9 years and older	Not applicable	One 0.5-mL dose (2.1)

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

Suspension for injection:

- 0.5-mL single-dose prefilled syringes (3)
- 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL). (3)

---------- CONTRAINDICATIONS ----------

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. (4, 11)

---------- WARNINGS AND PRECAUTIONS ----------

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

---------- ADVERSE REACTIONS ----------

- In adults who received FLULAVAL, the most common (≥10%) solicited local adverse reactions were pain (51%), redness (13%), and/or swelling (11%); the most common solicited systemic adverse events were fatigue (20%), headache (18%), and muscle aches/arthralgia (18%). (6.1)
- In children aged 3 through 17 years who received FLULAVAL, the most common (≥10%) solicited local adverse reaction was pain (56%). (6.1)
- In children aged 3 through 4 years who received FLULAVAL, the most common (≥10%) solicited systemic adverse events were irritability (25%), drowsiness (19%), and loss of appetite (16%). (6.1)
- In children aged 5 through 17 years who received FLULAVAL, the most common (≥10%) solicited systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%). (6.1)
- In children aged 6 through 35 months who received FLULAVAL QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (40%); most common solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite (29%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS ----------

- Geriatric Use: Antibody responses were lower in geriatric subjects who received FLULAVAL than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLULAVAL® is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FLULAVAL is approved for use in persons aged 6 months and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

The dose and schedule for FLULAVAL are presented in Table 1.

Table 1. FLULAVAL: Dosing

Age	Vaccination Status	Dose and Schedule
6 months through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each)
9 years and older	Not applicable	One 0.5-mL dose

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart.

2.2 Administration Instructions

Shake well before administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Attach a sterile needle to the prefilled syringe and administer intramuscularly.

For the multi-dose vial, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose from the multi-dose vial and administer intramuscularly. A sterile syringe with a needle bore no larger than 23 gauge is recommended for administration. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial**.**

Between uses, return the multi-dose vial to the recommended storage conditions, between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Once entered, a multi-

dose vial, and any residual contents, should be discarded after 28 days.

The preferred sites for intramuscular injection are the anterolateral thigh for children aged 6 through 11 months and the deltoid muscle of the upper arm for persons aged 12 months and older. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously, intradermally, or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLULAVAL is a suspension for injection available in 0.5-mL prefilled TIP-LOK® syringes and 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL).

4 CONTRAINDICATIONS

Do not administer FLULAVAL to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case/one million persons vaccinated.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of FLULAVAL.

5.4 Altered Immunocompetence

If FLULAVAL is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent

persons.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL may not protect all susceptible individuals.

5.6 Persons at Risk of Bleeding

As with other intramuscular injections, FLULAVAL should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of hematoma following the injection.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the possibility that broad use of FLULAVAL could reveal adverse reactions not observed in clinical trials.

In adults who received FLULAVAL, the most common (≥10%) solicited local adverse reactions were pain (51%), redness (13%), and swelling (11%); the most common (≥10%) solicited systemic adverse events were fatigue (20%), headache (18%), and muscle aches/arthralgia (18%).

In children aged 3 through 17 years who received FLULAVAL, the most common (≥10%) solicited local adverse reaction was pain (56%). In children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse events were irritability (25%), drowsiness (19%), and loss of appetite (16%). In children aged 5 through 17 years, the most common (≥10%) systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%).

In children aged 6 through 35 months who received FLULAVAL® QUADRIVALENT, the most common (≥10%) solicited local adverse reaction was pain (40%); the most common (≥10%) solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite (29%).

<u>FLULAVAL in Adults</u>

Safety data were obtained from 3 randomized, controlled trials, one of which was a placebo-controlled efficacy trial. In these trials, 9,836 subjects were randomized to receive either FLULAVAL (5,114 subjects in the safety analysis), FLUZONE®, a U.S.-licensed trivalent, inactivated influenza vaccine, manufactured by Sanofi Pasteur Inc. (894 subjects in the safety analysis), or placebo (3,828 subjects in the safety analysis), intramuscularly. In these trials, solicited events were collected for 4 days (i.e., 30 minutes post-vaccination through the next 3 days). Unsolicited adverse events that occurred within 22 days of vaccination (Day 0 to 21)

were recorded based on spontaneous reports or in response to queries about changes in health status.

Trial 1 (NCT01389479) (Immunogenicity): Safety information was collected in a randomized, controlled US trial. This trial included 1,000 adults aged 18 through 64 years who were randomized to receive FLULAVAL (n = 721) or a U.S.-licensed trivalent, inactivated influenza vaccine (n = 279). Among recipients of FLULAVAL, 57% were female; 91% of subjects were white and 9% were of other racial/ethnic groups. The mean age of subjects was 38 years; 80% were aged 18 through 49 years and 20% were aged 50 through 64 years.

Trial 2 (NCT00232947) (Immunogenicity Non-Inferiority): Safety information was collected in a randomized, double-blind, active-controlled U.S. trial. The trial included 1,225 adults aged ≥50 years randomized to receive FLULAVAL (n = 610) or a U.S.-licensed trivalent, inactivated influenza vaccine (n = 615). In the total population, 57% were female; 95% of subjects were white and 5% were of other racial/ethnic groups. The mean age of subjects was 66 years; 46% were aged 50 through 64 years, 41% were aged 65 through 79 years, and 13% were aged ≥80 years.

Trial 3 (NCT00216242) (Efficacy): Safety information was collected in a double-blind, placebo-controlled U.S. trial. The trial included 7,658 adults aged 18 through 49 years randomized to receive FLULAVAL (n = 3,807) or placebo (n = 3,851). In the total population, 61% were female; 84% of subjects were white, 10% black, 2% Asian, and 4% were of other racial/ethnic groups. The mean age of subjects was 33 years.

Solicited Adverse Events: Solicited local adverse reactions and systemic adverse events collected for 4 days (day of vaccination and the next 3 days) are presented in Table 2.

Table 2. FLULAVAL: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of Vaccination in Adults (Total Vaccinated Cohort)

	Percentage of Subjects Reporting Event											
	Trial 1[b] Aged 18 through 64 Years				Trial 2[b] Aged 50 Years and Older				Trial 3[b] Aged 18 through 49 Years			
	FLULAVAL n = 721		Comparator[c] n = 279		FLULAVAL n = 610		Comparator[c] n = 615		FLULAVAL n = 3,783		Placebo n = 3,828	
	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]	Any	Gr 3[d]
Local Adverse Reactions												
Pain	24.1	0.0	30.5	0.4	24.9	0.0	31.7	0.0	51.1	0.2	13.8	<0.1
Redness	10.5	0.1	10.0	0.0	9.7	0.2	10.6	0.2	12.6	0.3	6.1	0.1
Swelling	9.8	0.1	10.4	0.4	6.9	0.3	9.4	0.5	11.0	0.3	2.8	0.0
Systemic Adverse Events												
Headache	17.6	0.4	17.2	0.0	11.0	0.2	12.0	0.3	18.1	0.6	18.7	0.5
Fatigue	17.1	0.3	15.4	0.0	12.0	0.2	13.0	0.5	20.1	0.6	17.7	0.4
Muscle aches[e]	12.9	0.4	15.8	0.0	11.0	0.2	10.2	0.0	18.3	0.2	10.2	0.2
Fever[f]	11.0	0.0	10.0	0.4	0.8	0.0	1.5	0.0	2.5	<0.1	1.4	0.1
Malaise	10.1	0.4	10.0	0.4	6.1	0.3	7.2	0.0	8.9	0.3	6.2	0.4
Sore throat	8.9	0.4	9.3	0.0	5.2	0.2	5.9	0.0	8.6	0.3	9.0	0.4
Reddened eyes	6.1	0.3	5.0	0.0	4.4	0.0	6.5	0.0	6.6	<0.1	6.0	<0.1
Cough	6.1	0.3	6.8	0.0	5.4	0.2	6.2	0.0	7.6	0.1	6.5	0.1
Chills	5.3	0.3	2.2	0.0	3.1	0.2	5.7	0.0	4.2	0.2	3.6	0.2
Chest tightness	3.3	0.0	1.4	0.0	2.5	0.3	2.1	0.0	3.4	<0.1	2.8	0.1
Facial swelling	1.0	0.0	0.4	0.0	1.3	0.0	1.6	0.0	1.3	0.0	1.0	0.0

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = number of subjects with diary card completed. Gr 3 = Grade 3.

[a] 4 days included day of vaccination and the subsequent 3 days.

[b] Trial 1: NCT01389479; Trial 2: NCT00232947; Trial 3: NCT00216242.

[c] U.S.-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] Grade 3 pain, headache, fatigue, muscle aches, malaise, sore throat, cough, chills, chest tightness: Defined as prevented work/school/normal activities.
Grade 3 redness, swelling: Defined as >50 mm. Grade 3 fever: Defined as >103.1°F (39.5°C).
Grade 3 reddened eyes: Defined as very reddened, interfered with vision or caused a doctor's visit. Grade 3 facial swelling: Defined as very swollen, prevented work/school/normal activities or caused a doctor's visit.

[e] For Trial 2 and Trial 3, includes muscle aches and arthralgia.
[f] Fever: Defined as ≥99.5°F (37.5°C).

Unsolicited Adverse Events: The incidence of unsolicited adverse events in the 21 days post-vaccination was comparable for FLULAVAL and the active comparator in Trial 1 (16% and 15%, respectively) and in Trial 2 (18% and 21%, respectively). In Trial 3, the incidence of unsolicited adverse events was comparable for the groups (21% for FLULAVAL and 19% for placebo).

Unsolicited adverse events defined as reported with FLULAVAL in >1.0% of subjects are described as follows: Trial 1: Cough, headache, and pharyngolaryngeal pain; Trial 2: Diarrhea, headache, and nasopharyngitis; and Trial 3: Pharyngolaryngeal pain, headache, fatigue, cough, injection site pain, upper respiratory tract infection, musculoskeletal pain, nasopharyngitis, injection site erythema, and discomfort.

Serious Adverse Events (SAEs): In Trial 1, no SAEs were reported. In Trial 2, 3% of subjects receiving FLULAVAL and 3% of subjects receiving the active comparator reported SAEs. In Trial 3, 1% of subjects receiving FLULAVAL and 1% of subjects receiving placebo reported SAEs. In the 3 clinical trials, the rates of SAEs were comparable between groups and none of the SAEs were considered related to vaccination.

<u>FLULAVAL in Children</u>

Trial 4 (NCT00980005) (Immunogenicity Non-Inferiority): An observer-blind, active-controlled U.S. trial evaluated subjects aged 3 through 17 years who received FLULAVAL (n = 1,055) or FLUZONE (n = 1,061), a U.S.-licensed trivalent, inactivated influenza vaccine, manufactured by Sanofi Pasteur Inc. In the overall population, 53% were male; 78% of subjects were white, 12% were black, 2% were Asian, and 8% were of other racial/ethnic groups. The mean age of subjects was 8 years. Children aged 3 through 8 years with no history of influenza vaccination received 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of influenza vaccination and children aged 9 years and older received one dose. Solicited local adverse reactions and systemic adverse events were collected for 4 days (day of vaccination and the next 3 days) (Table 3).

Table 3. FLULAVAL: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of First Vaccination in Children Aged 3 through 17 Years[b] (Total Vaccinated Cohort)

	FLULAVAL %		Active Comparator[c] %	
	Any	Grade 3[d]	Any	Grade 3[d]
	Aged 3 through 17 Years			
Local Adverse Reactions	**n = 1,042**		**n = 1,026**	
Pain	55.9	1.9	53.0	2.0
Redness	4.0	0.2	4.5	0.0
Swelling	4.4	0.1	4.9	0.0
	Aged 3 through 4 Years			
Systemic Adverse Events	**n = 293**		**n = 279**	
Irritability	25.3	1.7	26.5	1.1
Drowsiness	18.8	1.4	18.6	0.4
Loss of appetite	16.0	2.4	13.3	0.4
Fever[e]	5.1	1.0	2.9	0.4
	Aged 5 through 17 Years			
Systemic Adverse Events	**n = 750**		**n = 747**	
Muscle aches	23.9	0.7	22.9	0.9
Headache	16.8	0.8	15.3	0.5
Fatigue	16.8	1.3	16.7	1.2
Arthralgia	7.7	0.3	9.5	0.3
Shivering	5.6	0.1	4.8	0.4
Fever[e]	4.5	1.6	4.1	1.5

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = number of subjects with diary card completed.

[a] 4 days included day of vaccination and the subsequent 3 days.

[b] Trial 4: NCT00980005.

[c] U.S.-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <5years), or pain that prevented normal activity (children ≥5 years).
Grade 3 swelling, redness: Defined as >100 mm.
Grade 3 irritability, drowsiness, muscle aches, headache, fatigue, arthralgia, shivering: Defined as prevented normal activity.
Grade 3 loss of appetite: Defined as not eating at all.
Grade 3 (or higher) fever: Defined as ≥102.2°F (39.0°C).

[e] Fever: Defined as ≥100.4°F (38.0°C)

In children who received a second dose of FLULAVAL or the comparator vaccine, the incidences of adverse events following the second dose were generally lower than those

observed after the first dose.

The incidence of unsolicited adverse events that occurred within 28 days (Day 0 to 27) of any vaccination reported in subjects who received FLULAVAL (n = 1,055) or FLUZONE (n = 1,061) was 40% and 37%, respectively. The unsolicited adverse events that occurred most frequently (≥0.1% of subjects for FLULAVAL) and considered possibly related to vaccination included diarrhea, influenza-like illness, injection site hematoma, injection site rash, injection site warmth, rash, upper abdominal pain, and vomiting. The rates of SAEs were comparable between groups (0.9% and 0.6% for FLULAVAL and the comparator, respectively); none of the SAEs were considered related to vaccination.

FLULAVAL QUADRIVALENT in Children

Safety data were obtained with FLULAVAL QUADRIVALENT in children aged 6 through 35 months. FLULAVAL QUADRIVALENT, an inactivated influenza vaccine that contains the hemagglutinins of 2 influenza A subtype viruses and 2 influenza type B viruses, is manufactured according to the same process as FLULAVAL.

Trial 5 (NCT02242643) was a randomized, observer-blind, active-controlled immunogenicity and safety trial. The trial included subjects aged 6 through 35 months who received FLULAVAL QUADRIVALENT (n = 1,207) or FLUZONE® QUADRIVALENT, a U.S.-licensed inactivated influenza vaccine (n = 1,217) used as comparator, manufactured by Sanofi Pasteur Inc. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or the comparator vaccine approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or the comparator vaccine. In the overall population, 53% were male; 64% were white, 16% were black, 3% were Asian, and 17% were of other racial/ethnic groups. The mean age of subjects was 20 months. Subjects were followed for safety for 6 months; solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days) postvaccination. The incidence of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in children are shown in Table 4.

Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] of First Vaccination in Children Aged 6 through 35 Months[b] (Total Vaccinated Cohort)

	FLULAVAL QUADRIVALENT %		Active Comparator[c] %	
	Any	Grade 3[d]	Any	Grade 3[d]
Local Adverse Reactions	**n = 1,151**		**n = 1,146**	
Pain	40.3	2.4	37.4	1.4
Swelling	1.0	0.0	0.4	0.0
Redness	1.3	0.0	1.3	0.0
Systemic Adverse Events	**n = 1,155**		**n = 1,148**	
Irritability	49.4	3.8	45.9	3.0
Drowsiness	36.7	2.7	36.9	2.6
Loss of appetite	28.9	1.6	28.6	1.3
Fever [e]	5.6	1.4	5.8	1.0

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available (i.e., diary card completed for solicited symptoms). n = number of subjects with diary card completed.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Trial 5: NCT02242643.

[c] U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful.
Grade 3 swelling, redness: Defined as >100 mm.
Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
Grade 3 drowsiness: Defined as prevented normal activity.
Grade 3 loss of appetite: Defined as not eating at all.
Grade 3 (or higher) fever: Defined as >102.2°F (39.0°C).

[e] Fever: Defined as ≥100.4°F (38.0°C).

In children who received a second dose of FLULAVAL QUADRIVALENT or the comparator vaccine, the incidences of solicited adverse events following the second dose were generally similar or lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 46% and 44% of subjects who received FLULAVAL QUADRIVALENT (n = 1,207) and the comparator vaccine (n = 1,217), respectively. The unsolicited adverse reactions that occurred most frequently (≥1%) for FLULAVAL QUADRIVALENT included upper respiratory tract infection, cough, diarrhea, pyrexia, vomiting, and rash. Serious adverse events occurring during the study period (approximately 6 months) were reported in 2% of subjects who received FLULAVAL

QUADRIVALENT and in 2% of subjects who received the comparator vaccine. There were no deaths reported during the study period.

6.2 Postmarketing Experience

In addition to reports in clinical trials, the following adverse events have been identified during postapproval use of FLULAVAL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence rate or establish a causal relationship to the vaccine. Adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to FLULAVAL.

Blood and Lymphatic System Disorders

Lymphadenopathy.

Eye Disorders

Eye pain, photophobia.

Gastrointestinal Disorders

Dysphagia.

General Disorders and Administration Site Conditions

Chest pain, injection site inflammation, asthenia, injection site rash, abnormal gait, injection site bruising, injection site sterile abscess.

Immune System Disorders

Allergic reactions including anaphylaxis, angioedema.

Infections and Infestations

Rhinitis, laryngitis, cellulitis.

Musculoskeletal and Connective Tissue Disorders

Muscle weakness, arthritis.

Nervous System Disorders

Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

Psychiatric Disorders

Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders

Dyspnea, dysphonia, bronchospasm, throat tightness.

Skin and Subcutaneous Tissue Disorders

Urticaria, pruritus, sweating.

Vascular Disorders

Flushing, pallor.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

FLULAVAL should not be mixed with any other vaccine in the same syringe or vial.

There are insufficient data to assess the concomitant administration of FLULAVAL with other vaccines. When concomitant administration of other vaccines is required, the vaccines should be administered at different injection sites.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to FLULAVAL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLULAVAL during pregnancy. Healthcare providers are encouraged to register women by calling 1-888-452-9622.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are insufficient data on FLULAVAL in pregnant women to inform vaccine-associated risks.

A developmental toxicity study was performed in female rats administered FLULAVAL prior to mating and during gestation. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to FLULAVAL *[see Data]*.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal

influenza are at increased risk of severe illness associated with influenza infection compared with non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: In a developmental toxicity study, female rats were administered FLULAVAL by intramuscular injection 4 weeks prior to mating, and on gestation Days 6, 8, 11, and 15. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether FLULAVAL is excreted in human milk. Data are not available to assess the effects of FLULAVAL on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLULAVAL and any potential adverse effects on the breastfed child from FLULAVAL or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of FLULAVAL in children younger than 6 months have not been established.

8.5 Geriatric Use

In clinical trials, there were 330 subjects aged 65 years and older who received FLULAVAL; 142 of these subjects were aged 75 years and older. Hemagglutination inhibition antibody responses were lower in geriatric subjects than younger subjects after administration of FLULAVAL. *[See Clinical Studies (14.2).]* Solicited adverse events were similar in frequency to those reported in younger subjects *[see Adverse Reactions (6.1)]*.

11 DESCRIPTION

FLULAVAL, Influenza Vaccine, for intramuscular injection, is a trivalent, split-virion, inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza viruses is produced and purified separately. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

FLULAVAL is a sterile, opalescent, translucent to off-white suspension in a phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon shaking to form a homogeneous suspension.

FLULAVAL has been standardized according to USPHS requirements for the xxxx-xxxx influenza season and is formulated to contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains: A/xxxx (H1N1), A/xxxx (H3N2), and B/xxxx.

The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each 0.5-mL dose from the multi-dose vial contains 50 mcg thimerosal (<25 mcg mercury); thimerosal, a mercury derivative, is added as a preservative.

Each 0.5-mL dose of either presentation may also contain residual amounts of ovalbumin (≤0.3 mcg), formaldehyde (≤25 mcg), sodium deoxycholate (≤50 mcg), α-tocopheryl hydrogen succinate (≤240 mcg), and polysorbate 80 (≤665 mcg) from the manufacturing process. Antibiotics are not used in the manufacture of this vaccine.

The tip caps and plungers of the prefilled syringes are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies, antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.[1,2] Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter.

Annual revaccination is recommended because immunity declines during the year after vaccination and because circulating strains of influenza virus change from year to year.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL has not been evaluated for carcinogenic, mutagenic potential, or male infertility in

animals. Vaccination of female rats with FLULAVAL had no effect on fertility *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

The effectiveness of FLULAVAL was demonstrated based on clinical endpoint efficacy data for FLULAVAL QUADRIVALENT (Influenza Vaccine), clinical endpoint efficacy data for FLULAVAL, and on an evaluation of serum HI antibody responses to FLULAVAL and FLULAVAL QUADRIVALENT.

14.1 Efficacy against Influenza

Efficacy Trial in Children

The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 6, a randomized, observer-blind, non-influenza vaccine-controlled trial conducted in 3 countries in Asia, 3 in Latin America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy subjects aged 3 through 8 years were randomized (1:1) to receive FLULAVAL QUADRIVALENT (n = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage) influenza strains, or HAVRIX® (Hepatitis A Vaccine) (n = 2,584), as a control vaccine. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or HAVRIX. In the overall population, 52% were male; 60% were Asian, 5% were white, and 35% were of other racial/ethnic groups. The mean age of subjects was 5 years.

Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease presenting as influenza-like illness (ILI). ILI was defined as a temperature ≥100°F in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine efficacy was calculated based on the ATP cohort for efficacy (Table 5).

Table 5. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children Aged 3 through 8 Years[a] (According-to-Protocol Cohort for Efficacy)

	N[b]	n[c]	Influenza Attack Rate % (n/N)	Vaccine Efficacy % (CI)
All RT-PCR-Positive Influenza				
FLULAVAL QUADRIVALENT	2,379	58	2.4	55.4[d] (95% CI: 39.1, 67.3)
HAVRIX[e]	2,398	128	5.3	–
All Culture-Confirmed Influenza[f]				
FLULAVAL QUADRIVALENT	2,379	50	2.1	55.9 (97.5% CI: 35.4, 69.9)
HAVRIX[e]	2,398	112	4.7	–
Antigenically Matched Culture-Confirmed Influenza				
FLULAVAL QUADRIVALENT	2,379	31	1.3	45.1[g] (97.5% CI: 9.3, 66.8)
HAVRIX[e]	2,398	56	2.3	–

CI = Confidence Interval; RT-PCR = Reverse transcriptase polymerase chain reaction.

[a] Trial 6: NCT01218308.

[b] According-to-protocol cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol-specified efficacy criteria.

[c] Number of influenza cases.

[d] Vaccine efficacy for FLULAVAL QUADRIVALENT met the pre-defined criterion of >30% for the lower limit of the 2-sided 95% CI.

[e] Hepatitis A Vaccine used as a control vaccine.

[f] Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched; 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with HAVRIX)].

[g] Since only 67% of cases could be typed, the clinical significance of this result is unknown.

In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI was evaluated in subjects aged 3 through 4 years and 5 through 8 years; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2),

respectively. As the trial lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

As a secondary objective in the trial, subjects with RT-PCR-positive influenza A and/or B were prospectively classified based on the presence of adverse outcomes that have been associated with influenza infection (defined as fever >102.2°F/39.0°C, physician-verified shortness of breath, pneumonia, wheezing, bronchitis, bronchiolitis, pulmonary congestion, croup and/or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complications, including myositis, encephalitis, seizure and/or myocarditis).

The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse outcomes had too few cases to calculate a risk reduction. The incidence of these adverse outcomes is presented in Table 6.

Table 6. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated with RT-PCR-Positive Influenza in Children Aged 3 through 8 Years[a] (Total Vaccinated Cohort)[b]

	FLULAVAL QUADRIVALENT n = 2,584			HAVRIX[c] n = 2,584		
Adverse Outcome[d]	**Number of Events**	**Number of Subjects[e]**	**%**	**Number of Events**	**Number of Subjects[e]**	**%**
Fever >102.2°F/39.0°C	16[f]	15	0.6	51[f]	50	1.9
Shortness of breath	0	0	0	5	5	0.2
Pneumonia	0	0	0	3	3	0.1
Wheezing	1	1	0	1	1	0
Bronchitis	1	1	0	1	1	0
Pulmonary congestion	0	0	0	1	1	0
Acute otitis media	0	0	0	1	1	0
Bronchiolitis	0	0	0	0	0	0
Croup	0	0	0	0	0	0
Encephalitis	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	0
Myositis	0	0	0	0	0	0
Seizure	0	0	0	0	0	0

[a] Trial 6: NCT01218308.

[b] Total vaccinated cohort included all vaccinated subjects for whom data were available.

[c] Hepatitis A Vaccine used as a control vaccine.

[d] In subjects who presented with more than one adverse outcome, each outcome was counted in the respective category.

[e] Number of subjects presenting with at least one event in each group.

[f] One subject in each group had sequential influenza due to influenza type A and type B viruses.

Efficacy Trial in Adults

The efficacy of FLULAVAL was evaluated in a randomized, double-blind, placebo-controlled trial conducted in the United States during the 2005-2006 and 2006-2007 influenza seasons (Trial 3). Efficacy of FLULAVAL was defined as the prevention of culture-confirmed influenza A and/or B cases, for vaccine antigenically matched strains, compared with placebo. Healthy subjects aged 18 through 49 years were randomized (1:1); a total of 3,783 subjects received FLULAVAL and 3,828 subjects received placebo *[see Adverse Reactions (6.1)]*. Subjects were monitored for influenza-like illnesses (ILI) starting 2 weeks post-vaccination and for duration of approximately 7 months thereafter. Culture-confirmed influenza was assessed by active and passive surveillance of ILI. Influenza-like illness was defined as illness sufficiently severe to limit daily activity and including cough, and at least one of the following: Fever >99.9°F, nasal congestion or runny nose, sore throat, muscle aches or arthralgia, headache, feverishness or chills. After an episode of ILI, nose and throat swab samples were collected for analysis; attack rates and vaccine efficacy were calculated using the per protocol cohort (Table 7). Of note, the 1.2% attack rate in the placebo group for culture-confirmed, antigenically matched strains was lower than expected, contributing to a wide confidence interval for the estimate of vaccine efficacy.

Table 7. FLULAVAL: Influenza Attack Rates and Vaccine Efficacy against Culture-confirmed Influenza in Adults Aged 18 through 49 Years[a] (Per Protocol Cohort)

			Influenza Attack Rates	**Vaccine Efficacy**	
	N[b]	**n[c]**	**% (n/N)**	**%**	**97.5% CI Lower Limit**
Antigenically Matched Strains					
FLULAVAL	3,714	23	0.6	46.3	9.8[d]
Placebo	3,768	45	1.2	–	–
All Culture-Confirmed Influenza (Matched, Unmatched, and Untyped)					
FLULAVAL	3,714	30	0.8	49.3	20.3
Placebo	3,768	60	1.6	–	–

CI = Confidence Interval.

[a] Trial 3: NCT00216242.

[b] Per Protocol Cohort for efficacy included subjects with no protocol deviations considered to

compromise efficacy data.

[c] Number of influenza cases.

[d] Lower limit of the one-sided 97.5% CI for vaccine efficacy against influenza due to antigenically matched strains was less than the pre-defined success criterion of ≥35%.

14.2 Immunological Evaluation

Adults

Trial 1 was a randomized, blinded, active-controlled US trial performed in healthy adults aged 18 through 64 years (N = 1,000). A total of 721 subjects received FLULAVAL, and 279 received a U.S.-licensed trivalent, inactivated influenza vaccine, FLUZONE (manufactured by Sanofi Pasteur Inc.), intramuscularly; 959 subjects had complete serological data and no major protocol deviations *[see Adverse Reactions (6.1)]*.

Analyses of immunogenicity (Table 8) were performed for each hemagglutinin (HA) antigen contained in the vaccine: 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the proportion of subjects with HI antibody titers of ≥1:40 after vaccination, and 2) assessment of the lower bounds of 2-sided 95% confidence intervals for rates of seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40). The pre-specified success criteria for HI titer ≥1:40 was 70% and for seroconversion rate was 40%. The lower limit of the 2-sided 95% CI for the percentage of subjects who achieved an HI titer of ≥1:40 exceeded the pre-defined criteria for the A strains. The lower limit of the 2-sided 95% CI for the percentage of subjects who achieved seroconversion exceeded the pre-defined criteria for all 3 strains.

Table 8. Immune Responses to Each Antigen 21 Days after Vaccination with FLULAVAL[a] in Adults Aged 18 through 64 Years (Per Protocol Cohort)[b]

	FLULAVAL N = 692 % of Subjects (95% CI)	
HI titers ≥1:40	**Pre-vaccination**	**Post-vaccination**
A/New Caledonia/20/99 (H1N1)	24.6	96.5 (94.9, 97.8)
A/Wyoming/03/03 (H3N2)	58.7	98.7 (97.6, 99.4)
B/Jiangsu/10/03	5.4	62.9 (59.1, 66.5)
Seroconversion[c] to:		
A/New Caledonia/20/99 (H1N1)	85.6 (82.7, 88.1)	
A/Wyoming/03/03 (H3N2)	79.3 (76.1, 82.3)	
B/Jiangsu/10/03	58.4 (54.6, 62.1)	

HI = hemagglutination inhibition; CI = Confidence Interval.

[a] Results obtained following vaccination with FLULAVAL manufactured for the 2004–2005 season.

[b] Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose HI titer data and no major protocol deviations.

[c] Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titers from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

Trial 2 (Immunogenicity Non-Inferiority): In a randomized, double-blind, active-controlled US trial, immunological non-inferiority of FLULAVAL was compared with a U.S.-licensed trivalent, inactivated influenza vaccine, FLUZONE, manufactured by Sanofi Pasteur Inc. A total of 1,225 adults aged 50 years and older in stable health were randomized to receive FLULAVAL or the comparator vaccine intramuscularly *[see Adverse Reactions (6.1)]*.

Analyses of immunogenicity were performed for each HA antigen contained in the vaccines: 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the geometric mean antibody titer (GMT) ratio (FLULAVAL/comparator), and 2) assessment of the lower bounds of 2-sided 95% confidence intervals for seroconversion rates (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40). Non-inferiority of FLULAVAL to the comparator vaccine was established for all 6 co-primary endpoints (Table 9). Within each age stratum, immunogenicity results were similar between the groups.

Table 9. Immune Responses to Each Antigen 21 Days after Vaccination with FLULAVAL Versus Comparator Influenza Vaccine in Adults Aged 50 Years and Older[a] (Per Protocol Cohort)[b]

	FLULAVAL n = 592	Active Comparator[c] n = 595	
GMTs Against	**GMT (95% CI)**	**GMT (95% CI)**	**GMT Ratio[d] (95% CI)**
A/New Caledonia/20/99 (H1N1)	113.4 (104.7, 122.8)	110.2 (101.8, 119.3)	1.03 (0.92, 1.15)
A/New York/55/04 (H3N2)	223.9 (199.5, 251.3)	214.6 (191.3, 240.7)	1.04 (0.89, 1.23)
B/Jiangsu/10/03	82.3 (74.7, 90.6)	97.1 (88.2, 106.8)	0.85 (0.74, 0.97)
Seroconversion[e] to:	**% of Subjects (95% CI)**	**% of Subjects (95% CI)**	**Difference in Seroconversion Rates[f] (95% CI)**
A/New Caledonia/20/99 (H1N1)	34 (30.0, 37.6)	32 (28.3, 35.9)	2 (-3.7, 7.0)
A/New York/55/04 (H3N2)	83 (80.3, 86.3)	82 (78.4, 84.6)	1 (-2.6, 6.1)
B/Jiangsu/10/03	53 (49.0, 57.1)	56 (51.6, 59.6)	-3 (-8.3, 3.1)

GMT = Geometric mean antibody titer; CI = Confidence Interval.

[a] Results obtained following vaccination with influenza vaccines manufactured for the 2005-2006 season.

[b] Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose HI titer data and no major protocol deviations.

[c] U.S.-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.).

[d] FLULAVAL met non-inferiority criteria based on GMTs (lower limit of 2-sided 95% CI for GMT ratio [FLULAVAL/comparator vaccine] ≥0.67).

[e] Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

[f] FLULAVAL met non-inferiority criteria based on seroconversion rates (lower limit of 2-sided 95% CI for difference of FLULAVAL minus the comparator vaccine ≥-10%).

Children

In Trial 4, the immune response of FLULAVAL (n = 987) was compared to FLUZONE, a U.S.-licensed trivalent, inactivated influenza vaccine (n = 979), manufactured by Sanofi Pasteur Inc., in an observer-blind, randomized trial in children aged 3 through 17 years. The immune responses to each of the antigens contained in FLULAVAL formulated for the 2009-2010 season were evaluated in sera obtained after one or 2 doses of FLULAVAL and were compared with those following the comparator influenza vaccine *[see Adverse Reactions (6.1)]*.

The non-inferiority endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the According-to-Protocol (ATP) cohort. FLULAVAL was non-inferior to the comparator influenza for all strains based on adjusted GMTs and seroconversion rates (Table 10).

Table 10. Immune Responses to Each Antigen 28 Days after Last Vaccination with FLULAVAL Versus Comparator Influenza Vaccine in Children Aged 3 through 17 Years[a] (According-to-Protocol Cohort for Immunogenicity)[b]

	FLULAVAL	**Active Comparator[c]**	
GMTs Against	**n = 987 (95% CI)**	**n = 979 (95% CI)**	**GMT Ratio[d] (95% CI)**
A/Brisbane (H1N1)	320.9 (298.3, 345.2)	329.4 (306.8, 353.7)	1.03 (0.94, 1.13)
A/Uruguay (H3N2)	414.7 (386.5, 444.9)	451.9 (423.8, 481.8)	1.05 (0.96, 1.13)
B/Brisbane	213.7 (198.5, 230.1)	200.2 (186.1, 215.3)	0.93 (0.85, 1.02)
Seroconversion[e] to:	**n = 987 % (95% CI)**	**n = 978 % (95% CI)**	**Difference in Seroconversion Rate[f] (95% CI)**
A/Brisbane (H1N1)	59.8 (56.6, 62.9)	58.2 (55.0, 61.3)	-1.6 (-5.9, 2.8)
A/Uruguay (H3N2)	68.2 (65.2, 71.1)	66.2 (63.1, 69.1)	-2.0 (-6.1, 2.1)
B/Brisbane	81.1 (78.5, 83.5)	78.6 (75.9, 81.2)	-2.4 (-6.0, 1.1)

GMT = Geometric mean antibody titer; CI = Confidence Interval.

[a] Results obtained following vaccination with influenza vaccines formulated for the 2009-2010 season.

[b] According-to-protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

[c] U.S.-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur Inc.).

[d] FLULAVAL met non-inferiority criteria based on GMTs (upper limit of 2-sided 95% CI for GMT ratio [comparator vaccine/FLULAVAL] ≤1.5).

[e] Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

[f] FLULAVAL met non-inferiority criteria based on seroconversion rates (upper limit of 2-sided 95% CI for difference of the comparator vaccine minus FLULAVAL ≤10%).

Trial 5 was a randomized, observer-blind, active-controlled trial in children aged 6 through 35 months which was conducted in the United States and Mexico. In this trial, subjects received 0.5 mL of FLULAVAL QUADRIVALENT containing 15 mcg HA of each of the four influenza strains included in the vaccine (n = 1,207); or 0.25 mL of control vaccine FLUZONE QUADRIVALENT (Influenza Vaccine) containing 7.5 mcg HA of each of the four influenza strains included in the vaccine (n = 1,217) *[see Adverse Reactions (6.1)]*.

Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 28 days following completion of vaccination regimen. Previously vaccinated children received one dose and previously unvaccinated children (i.e., unprimed individuals) received 2 doses 4 weeks apart of FLULAVAL QUADRIVALENT or the comparator. The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the ATP cohort. FLULAVAL QUADRIVALENT was non-inferior to the comparator for all 4 vaccine strains based on adjusted GMTs and seroconversion rates (Table 11).

Table 11. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Comparator Quadrivalent Influenza Vaccine at 28 Days Post-vaccination in Children Aged 6 through 35 Months[a] (According-to-Protocol Cohort for Immunogenicity)[b]

	FLULAVAL QUADRIVALENT[c]	Active Comparator[d]
Adjusted Geometric Mean Titers Against	**n = 972-974**	**n = 980**
A/California/07/2009 (H1N1)	99.6[e]	85.1
A/Texas/50/2012 (H3N2)	99.8[e]	84.6
B/Massachusetts/02/2012 (Yamagata lineage)	258.1[e]	167.3
B/Brisbane/60/2008 (Victoria lineage)	54.5[e]	33.7
Seroconversion[f] to:	**n = 972-974 % (95% CI)**	**n = 980 % (95% CI)**
A/California/07/2009 (H1N1)	73.7[e] (70.8, 76.4)	67.3 (64.3, 70.3)
A/Texas/50/2012 (H3N2)	76.1[e] (73.3, 78.8)	69.4 (66.4, 72.3)
B/Massachusetts/02/2012 (Yamagata lineage)	85.5[e] (83.2, 87.7)	73.8 (70.9, 76.5)
B/Brisbane/60/2008 (Victoria lineage)	64.9[e] (61.8, 67.9)	48.5 (45.3, 51.6)

CI = Confidence Interval.

[a] Trial 5: NCT02242643.

[b] According-to-protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

[c] A 0.5-mL dose containing 15 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

[d] A 0.25-mL dose of U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.) containing 7.5 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

[e] Non-inferior to the comparator vaccine based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (comparator/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper limit of the 2-sided 95% CI on difference of comparator vaccine minus FLULAVAL QUADRIVALENT ≤10%).

[f] Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

15 REFERENCES

1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103:133-138.
2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLULAVAL is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes (packaged without needles) and in 5-mL multi-dose vials containing 10 doses (0.5-mL each).

NDC xxxxx-xxx-xx Syringe in Package of 10: NDC xxxxx-xxx-xx

NDC xxxxx-xxx-xx Multi-Dose Vial (containing 10 doses) in Package of 1: NDC xxxxx-xxx-xx

Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light. Once entered, a multi-dose vial should be discarded after 28 days.

17 PATIENT COUNSELING INFORMATION

Provide the following information to the vaccine recipient or guardian:

- Inform of the potential benefits and risks of immunization with FLULAVAL.
- Educate regarding potential side effects, emphasizing that: (1) FLULAVAL contains non-infectious killed viruses and cannot cause influenza, and (2) FLULAVAL is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- Encourage women exposed to FLULAVAL during pregnancy to enroll in the pregnancy registry *[see Use in Specific Populations (8.1)*.
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

- Instruct that annual revaccination is recommended.

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