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Important Safety Information

Flublok Quadrivalent vaccine should not be administered to anyone who has had a severe allergic reaction (eg, anaphylaxis) to a previous dose of the vaccine or any component of the vaccine.

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Flublok Quadrivalent vaccine should be based on careful consideration of the potential benefits and risks.

The most common local adverse reactions to Flublok Quadrivalent vaccine include tenderness and pain at the injection site. The most common systemic reactions include headache, fatigue, myalgia, and arthralgia. Other adverse reactions may occur. Vaccination with Flublok Quadrivalent vaccine may not protect all individuals. Before administering Flublok Quadrivalent vaccine, please see accompanying full Prescribing Information on pages 21–26.

Flublok® Quadrivalent (Influenza Vaccine)

Proven to provide 30% to 43% better protection compared to a standard-dose quadrivalent inactivated influenza vaccine in persons 50 years of age and older.[1,2]

US Food and Drug Administration–approved indication

Flublok Quadrivalent vaccine is indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vaccine. Flublok Quadrivalent vaccine is approved for use in persons 18 years of age and older.

Contents

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Please see INDICATION and IMPORTANT SAFETY INFORMATION and accompanying FULL PRESCRIBING INFORMATION.

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The Product Profiler

The Product Profiler publication provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about clinical studies, FDA-approved indications, safety, efficacy, immunogenicity, and burden of disease information in a convenient package. Articles are written by experts in the field.

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PRODUCT PROFILER

Flublok® Quadrivalent (Influenza Vaccine)

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EXECUTIVE SUMMARY

This Product Profiler introduces new, important efficacy data for Flublok Quadrivalent vaccine. Flublok vaccine (trivalent) was first approved in 2013 and Flublok Quadrivalent vaccine was approved in 2016.[1,3] The new data shared in this Profiler were published in the *New England Journal of Medicine (NEJM)* in June 2017 and demonstrate that Flublok Quadrivalent vaccine provided 30% to 43% better protection against influenza disease compared to a standard-dose quadrivalent inactivated influenza vaccine (SD-IIV4) in persons 50 years of age and older, which includes the group that bears the greatest burden of severe influenza disease, persons 65 years of age and older.[1,2,4-6]

Flublok Quadrivalent vaccine is indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses in persons 18 years of age and older.[1] Flublok Quadrivalent vaccine contains 3 times the hemagglutinin (HA) of SD-IIV4, but retains a safety profile consistent with SD-IIV4.[3] The vaccine is produced through recombinant technology, which yields HA that is genetically identical to that associated with selected influenza strains, without the need for egg proteins, formaldehyde, antibiotics, or preservatives.[2]

In the aforementioned efficacy study, 9003 subjects 50 years of age and older were randomized to receive either Flublok Quadrivalent vaccine or SD-IIV4 (Fluarix® Quadrivalent Influenza Vaccine, GlaxoSmithKline).[4] Flublok Quadrivalent vaccine provided 30% better protection against PCR-confirmed, protocol-defined, influenza-like illness due to any influenza virus or subtype compared to SD-IIV4.[1,2] Additionally, Flublok Quadrivalent vaccine provided 43% better protection against culture-confirmed, protocol-defined, influenza-like illness due to any influenza virus or subtype compared to SD-IIV4.[1,2]

In a second trial in 1350 persons 18 through 49 years of age, which compared Flublok Quadrivalent vaccine to the same SD-IIV4, Flublok Quadrivalent vaccine was noninferior to the comparator vaccine for 3 of 4 influenza vaccine strains as assessed by seroconversion rates and geometric mean titers (GMT).[7] Safety and immunogenicity were largely comparable in this study.[1]

The annual economic burden of seasonal influenza, evaluated using 2003 US population demographics and dollars, was estimated to be $87 billion, with persons 50 through 64 years of age and 65 years of age and older accounting for 85% of that figure.[8]

Rates of hospitalization and mortality attributable to influenza are highest in those 50 years of age and older.[9] In this age group, 70% have at least 1 chronic condition and nearly 50% have 2 or more chronic conditions.[10] The majority of adults hospitalized for influenza have at least 1 comorbid condition.[11-15] Influenza infection is associated with increased rates of cardiovascular events, including acute myocardial infarction and coronary deaths, and the risk increases with advancing age.[16,17] Persons with diabetes are also at risk for serious complications and have an increased risk of influenza-related hospitalization.[18,19]

Influenza vaccination has been shown to be effective in the reduction of influenza-related morbidity, mortality, and associated health care costs,[20,21] and remains the key strategy for preventing influenza and its complications.[22,23] Despite these facts and the Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices' (ACIP's) 2010 recommendation for universal influenza immunization for persons 6 months of age and older,[24] results from the 2016 National Health Interview Survey (NHIS) indicate that only 45.4% of persons 50 through 64 years of age, and 65.3% of persons 65 years of age and older received an influenza vaccination in the previous year.[25]

In a study conducted in the 2014-2015 influenza season, Flublok Quadrivalent vaccine prevented 30% to 43% more cases of influenza in persons 50 years of age and older compared with SD-IIV4.[1,2] Therefore, this vaccine may be an especially important option to providers when immunizing this age group, which has 1 of the highest rates of influenza-related hospitalizations and mortalities,[9] coupled with a vaccination rate ranging from 45% to 65%.[25] Provider and patient access to Flublok Quadrivalent vaccine will be important in the 2018-2019 and future influenza immunizing seasons.

Key Facts

- Influenza, combined with pneumonia, is the eighth leading cause of death in the United States[26]
- Persons with 1 or more comorbid conditions are more likely to suffer influenza-related complications that may lead to hospitalization or death
  - 70% of persons 50 years of age and older suffer from 1 or more chronic conditions[10]
- New data, published in June 2017, demonstrated that Flublok Quadrivalent vaccine provided 30% to 43% better protection against influenza disease in persons 50 years of age and older compared to SD-IIV4. This age group contains people at increased risk for influenza-related complications[1,2,4]

  - Flublok Quadrivalent vaccine demonstrated 30% better protection in preventing PCR-confirmed, influenza-like illness caused by any viral type/subtype (95% confidence interval [CI], 10% to 47%) compared to SD-IIV4[1,2]
  - Flublok Quadrivalent vaccine showed 43% better protection in preventing culture-confirmed, influenza-like illness caused by any viral type/subtype (95% CI, 21% to 59%)[1,2]
- Recombinant technology yields HA, which is genetically identical to that associated with the influenza strains recommended annually by the Food and Drug Administration's (FDA's) Vaccines and Related Biological Products Advisory Committee (VRBPAC), and does not include egg proteins, formaldehyde, antibiotics, or preservatives[2,27]
- Flublok Quadrivalent vaccine had a comparable safety and immunogenicity profile compared to comparator vaccines in both studies
- Flublok vaccine (trivalent) was first approved in 2013 and Flublok Quadrivalent vaccine was approved in 2016 and includes 3 times the HA antigen of an SD-IIV4[1,3]
- Flublok Quadrivalent vaccine was acquired and will be distributed by Sanofi Pasteur in the 2018-2019 influenza season[28]
- The trivalent formulation of Flublok vaccine is no longer manufactured
- Flublok Quadrivalent vaccine has a unique CPT®[a] code, 90682[29]

INTRODUCTION

This Product Profiler introduces health care professionals and payers to newly published data for Flublok Quadrivalent vaccine. Flublok vaccine (trivalent) was first approved in 2013 and Flublok Quadrivalent vaccine was approved in 2016.[1,3] It provides background information on influenza disease, including complications of the disease and the economic and societal burdens of the disease.

Flublok Quadrivalent vaccine is indicated for persons 18 years of age and older, for active immunization against disease caused by 4 different influenza viruses: 2 influenza A subtype viruses and 2 influenza type B viruses covered by the vaccine.[1] Results of a study recently published in the *NEJM* demonstrate that Flublok Quadrivalent vaccine provided 30% to 43% better protection from laboratory, protocol-defined, influenza-like illness compared with SD-IIV4.[2] More detail on this study can be found in the Clinical Studies section of this Profiler.

Influenza is a contagious viral respiratory disease typically characterized by fever, cough, sore throat, runny or stuffy nose, muscle or body ache, headache, and fatigue.[23] Since 2010, influenza is estimated to affect 9.2 to 35.6 million individuals each year in the United States.[30] The severity of influenza disease varies widely from season to season and is influenced by a variety of factors including the predominant circulating influenza viral strains, the number of people immunized against influenza, and how well the influenza vaccine is matched to the strains.[30]

Influenza infection can cause substantial morbidity, leading to hospitalization and death.[30] Influenza affects all age groups, but the very young, older persons, pregnant women, and those with underlying health problems are at increased risk for complications (eg, bacterial pneumonia, worsening of comorbidities).[23] Discussed in more detail in the Influenza and Comorbidities section of this Profiler, influenza infection is also associated with increased rates of cardiovascular events.[16,31]

According to the CDC, the most effective method of protection against influenza disease and its complications is through annual influenza vaccination.[23] The ACIP of the CDC recommends annual influenza vaccination for all individuals 6 months of age and older who do not have any contraindications; no product is preferentially recommended over another.[24]

About Flublok Quadrivalent Vaccine

Flublok Quadrivalent vaccine is the only recombinant protein-based influenza vaccine approved by the US FDA.[32] Flublok Quadrivalent vaccine contains 3 times the hemagglutinin (HA) of SD-IIV4, but retains a safety profile consistent with standard-dose, quadrivalent, inactivated influenza vaccine (SD-IIV4).[2,32] The vaccine is produced through recombinant technology which yields HA that is genetically identical to that associated with selected influenza strains recommended annually by the FDA's VRBPAC.[2,27] The production process does not include egg proteins, formaldehyde, antibiotics, or preservatives.[32]

Indications and Usage

Flublok Quadrivalent vaccine is indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent vaccine is approved for use in persons 18 years of age and older.[1]

Clinical Trials

The efficacy and safety of Flublok Quadrivalent vaccine

[a]CPT (Current Procedural Terminology) is a registered trademark of the American Medical Association.

compared with SD-IIV4 (Fluarix Quadrivalent vaccine, GlaxoSmithKline) were evaluated in a phase 3/4, randomized, double-blind study (NCT02285998) of healthy persons 50 years of age and older who were medically stable or living independently without clinically significant acute illness.[1,2] Immunogenicity and safety of Flublok Quadrivalent vaccine were compared with SD-IIV4 in healthy persons 18 through 49 years of age in a phase 3, randomized, observer-blind study (NCT02290509).[1,33] Both studies were conducted during the 2014-2015 influenza season.[1,2]

Efficacy Conclusions (NCT02285998)[1,2]

The primary efficacy endpoint in the study of persons 50 years of age and older was polymerase chain reaction (PCR)-confirmed, protocol-defined, influenza-like illness caused by any strain beginning 2 weeks after vaccination. There were 8604 individuals (Flublok Quadrivalent vaccine, n=4303; SD-IIV4, n=4301) included in the efficacy analysis. The influenza attack rate among Flublok Quadrivalent vaccine recipients was 2.2% and among SD-IIV4 recipients was 3.2%. Flublok Quadrivalent vaccine, relative to SD-IIV4, demonstrated 30% better protection in preventing PCR-confirmed, influenza-like illness caused by any viral type/subtype (95% confidence interval [CI], 10% to 47%) and 43% better protection with respect to a secondary efficacy endpoint: culture-confirmed, influenza-like illness caused by any viral type/subtype (95% CI, 21% to 59%). Additional data from this study are available in the Clinical Trials section of this Profiler.

Immunogenicity Conclusions (NCT02290509 and NCT02285998)[1,4,33]

In the study of persons 18 through 49 years of age, hemagglutination inhibition was evaluated at 2 time points, pre-vaccination and 28 days after administration of a single dose of the vaccine. The immunogenicity analysis included evaluation of seroconversion[a] rates (SCRs) and GMT ratios for the 4 antigens (A/H1N1, AH3N2, B/Yamagata, and B/Victoria) included in the vaccines. A total of 1292 subjects (Flublok Quadrivalent vaccine, n=969; SD-IIV4, n=323) were evaluable for immune responses. The SCRs and GMT ratios of Flublok Quadrivalent vaccine were noninferior to those for SD-IIV4 for 3 of the 4 antigens. The B/Victoria lineage responses were low in both groups for both measures, making comparisons uninterpretable. Additional data from this study are available in the Clinical Trials section of this Profiler.

In the study of persons 50 years of age and older, serum samples for HAI titers were obtained on Day 0 prior to vaccination and on Day 28 after vaccination. The immunogenicity analysis included evaluation of SCRs and GMT ratios for 4 antigens (A/H1N1, A/H3N2, a B/Yamagata lineage strain, and a B/Victoria lineage strain) covered by the vaccines. SCRs for Flublok Quadrivalent vaccine recipients met the criterion for noninferiority for 2 of the 4 antigens (A/H3N2 and the B/Yamagata lineage strain). The postvaccination HAI GMTs showed robust immune responses to 3 of the 4 antigens (A/H1N1, A/H3N2, and the B/Yamagata lineage strain) and that the GMT ratios met the criterion for noninferiority for those 3 antigens. Additional data from this study are available in the Clinical Trials section of this Profiler.

[a]Seroconversion was defined as either a prevaccination hemagglutination inhibition (HAI) titer of <1:10 and a postvaccination HAI titer of ≥1:40, or a prevaccination HAI titer of ≥1:10 and a minimum 4-fold rise in postvaccination HAI titer, at Day 28.

Safety Conclusions[1,2,33]

In both Flublok Quadrivalent vaccine clinical trials, local and systemic reactions were reported for 7 days following vaccination, unsolicited adverse events collected for 28 days following vaccination, and serious adverse events recorded for 6 months post-vaccination. The safety profiles of Flublok Quadrivalent vaccine and SD-IIV4 were similar. Most unsolicited adverse events were mild to moderate in severity in both studies, and none were considered related to Flublok Quadrivalent vaccine. Serious adverse event rates were similar between both vaccine groups, and none were considered related to either study vaccine. Additional data are available in the Clinical Trials section of this Profiler.

Indication and Important Safety Information for Flublok Quadrivalent Vaccine[1]

Indication

Flublok Quadrivalent vaccine is indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent vaccine is approved for use in persons 18 years of age and older.

Important Safety Information

Flublok Quadrivalent vaccine should not be administered to anyone who has had a severe allergic reaction (eg, anaphylaxis) to a previous dose of the vaccine or any component of the vaccine.

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Flublok Quadrivalent vaccine should be based on careful consideration of the potential benefits and risks.

The most common local adverse reactions to Flublok Quadrivalent vaccine include tenderness and pain at the injection site. The most common systemic reactions include headache, fatigue, myalgia, and arthralgia. Other adverse reactions may occur. Vaccination with Flublok Quadrivalent vaccine may not protect all individuals.

Before administering Flublok Quadrivalent vaccine, please see accompanying full Prescribing Information.

INFLUENZA DISEASE

Seasonal influenza is a highly contagious respiratory infection caused by influenza A and B viruses.[22] In the US, seasonal influenza activity typically starts to increase in October, peaks between December and February, and can last through May.[22] The virus is transmitted from person-to-person via contaminated respiratory droplets produced when infected individuals cough, sneeze, or talk.[6,23,34] Influenza can enter through the mouths or noses of people who are nearby.[23] Although less common, the virus can also spread if a person comes into direct contact with infected respiratory secretions and then touches their mouth, nose, or possibly eyes.[6,23] Susceptibility to infection depends on an individual's preexisting immunity to a particular strain of influenza.[35] The incubation period for influenza ranges from 1 to 4 days.[6,23] An infected individual is contagious as early as 1 day before developing symptoms and up to 5 to 7 days after becoming sick, with people being the most contagious at 3 to 4 days.[23] Children and immunocompromised individuals can shed virus for longer than healthy persons 18 years of age and older.[36,37]

Symptoms and At-risk Populations

Presentation of influenza infection usually starts suddenly with individuals experiencing fever, cough (usually nonproductive), sore throat, runny or stuffy nose, myalgia (muscle or body ache), headache, and/or fatigue.[6,23,34] Fevers typically last at least 3 days and usually range from 100.4°F to 104°F, but they can be as high as 105.8°F in the first 24 hours.[6,34] Symptoms often improve within about 7 days, but cough and malaise may be present for weeks.[6,34] Estimates of asymptomatic infection range from 30% to 50% of cases of influenza infection.[6,22,38]

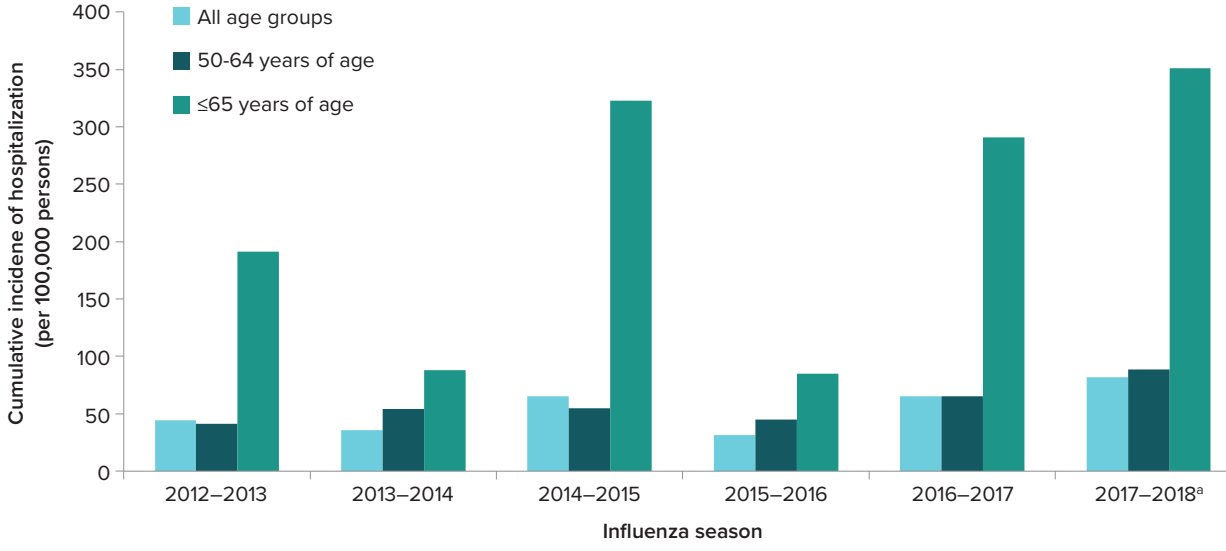
Influenza infection may result in asymptomatic to severe illness.[23] Most healthy people recover without complications, but the very young, older persons, pregnant women, and those with underlying health problems, which are often exacerbated by infection, are at increased risk for complications.[5,6]

Morbidity and Mortality

Influenza is 1 of the leading causes of morbidity and mortality worldwide, and influenza-related complications contribute greatly to this burden.[6] Common serious complications of influenza infection include secondary bacterial pneumonia and exacerbation of underlying chronic pulmonary and cardiopulmonary diseases, such as chronic obstructive pulmonary disease, asthma, chronic bronchitis, and congestive heart failure.[6,22,34] Influenza infection can also lead to exacerbation of diabetes, renal disease, hemo-

FIGURE 1

Incidence of laboratory-confirmed, influenza-associated hospitalizations[11-15,39]



[a]For the period from October 1, 2017 to February 24, 2018.

globinopathies, and underlying cardiac disease as well as development of myocarditis and pericarditis.[6,34] Neurological complications associated with influenza infection can include Reye's syndrome, encephalomyelitis, transverse myelitis, Guillain-Barré syndrome, aseptic meningitis, and encephalitis. Though rare, myositis and rhabdomyolysis have also been observed.[34]

Estimates of the annual number of influenza-associated deaths in the US ranged from 3349 to 48,614 between the years 1976 and 2007,[40] reaching a high of 56,000 during the 2012-2013 influenza season.[41] Persons 65 years of age and older followed by persons 50 through 64 years of age are most affected.[42] Together with pneumonia, influenza represents the eighth leading cause of death in the US.[26] Hospitalizations attributed to influenza are also common in the US, occurring in 140,000 to 710,000 individuals per year since 2010.[30] Rates of hospitalization, like mortality, are also highest in persons 65 years of age and older and 50 through 64 years of age (**Figure 1**).[9] It is estimated that more than one third of hospitalizations and about 10% of deaths occur among individuals younger than 65 years of age.[9,22]

Influenza and Comorbidities

The correlation between influenza and its effect on chronic conditions has been extensively studied. The majority of persons 18 years of age and older hospitalized for influenza have at least 1 comorbid condition.[11-15] By 50 years of age, 70% have been diagnosed with at least 1 chronic condition and 50% have 2 or more chronic conditions, including conditions that increase one's risk for influenza-related complications.[10] This helps explain why, prior to the CDC's 2010 recommendation for universal influenza vaccination, vaccination was already recommended for persons 50 years of age and older.[24,43] The most common chronic conditions in this age group are cardiovascular diseases and metabolic disorders, which affected 52% and 44% of this population, respectively, during the 2016-2017 influenza season.[15]

Influenza infection is associated with increased rates of cardiovascular events, including acute myocardial infarction and coronary deaths.[16,17,31] Evidence suggests the risk of acute myocardial infarction in patients 40 years of age and older is greatest within 1 to 3 days after acute respiratory infection.[16] Furthermore, the risk tends to increase with advancing age, and is greatest when the acute respiratory infection is caused by influenza infection.[16,17] Influenza epidemics are also associated with increased mortality resulting from acute myocardial infarction and chronic ischemic heart disease.[31]

Individuals with type 1 or type 2 diabetes are at risk for serious influenza-related complications, including pneumonia, bronchitis, sinus and ear infections, and exacerbation of diabetes symptoms.[18] These complications can occur in people whose diabetes is well controlled.[18] The presence of diabetes significantly increases the risk of influenza-related hospitalization.[44] In a UK-based cohort study conducted over a 7-year period between 2003–2004 and 2009–2010 of persons 18 years of age and older with type 2 diabetes, influenza vaccination was associated with significant reductions in hospital admission rates for stroke (30%), heart failure (22%), pneumonia or influenza (15%), and all-cause death (24%).[45] A Taiwanese-based cohort study of persons 65 years

FIGURE 2

Impact of influenza vaccination on major cause-specific mortality in persons 65 years of age and older[46]

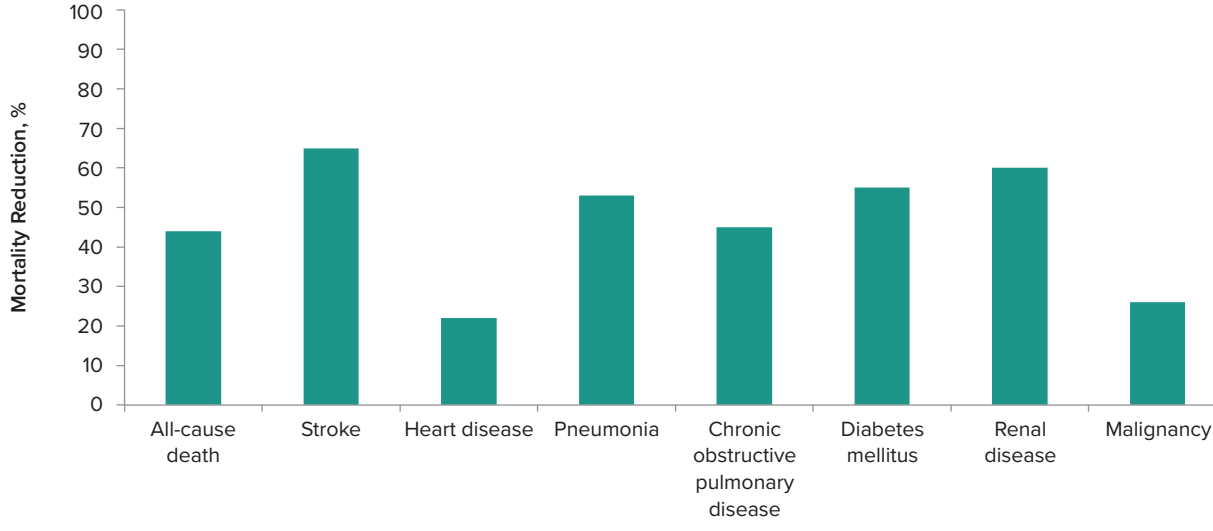
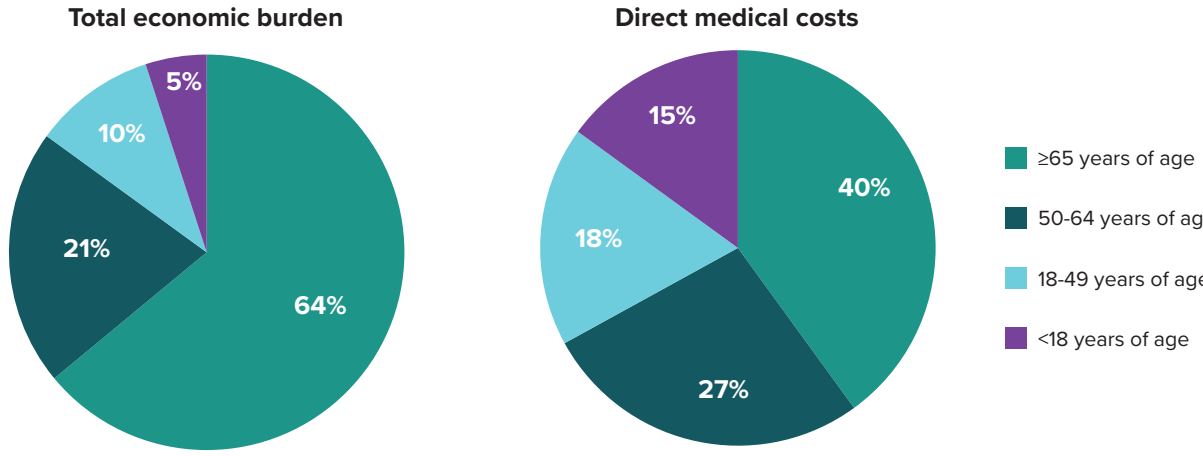


FIGURE 3
Total economic burden and direct medical costs by age group based on 2003 US population and dollars[8]



of age and older over a 10-month period in 2001 further demonstrated that influenza vaccination was associated with a significant reduction in mortality from stroke (65%) and from diabetes mellitus (55%) (**Figure 2**).[46]

Economic Burden

Molinari and colleagues reviewed epidemiological data to estimate the number of influenza-associated illnesses leading to outpatient visits, hospitalization, mortality, and work absenteeism or premature death, demonstrating the significant economic burden of influenza epidemics.[8] Applying health insurance claims and projected earnings or statistical life values, they estimated health care resource utilization associated with influenza infection.[8] Based on the 2003 US population demographics and dollars, the overall annual economic burden of the seasonal influenza epidemic was estimated to be $87 billion, which includes about 44 million days of lost productivity.[8] Persons 65 years of age and older accounted for 64% of the overall annual cost and 40% of direct medical costs, and those 50 through 64 years of age accounted for 21% and 27%, respectively (**Figure 3**).[8]

INFLUENZA VACCINATION AND CURRENT IMMUNIZATION RATES

Vaccination is the fundamental strategy for preventing influenza and its complications.[22,23] Influenza vaccination is proven to be highly effective at reducing influenza-related morbidity, mortality, and associated health care costs, specifically in older persons and high-risk populations.[6,8,20,21]

Of note, influenza vaccination may provide protection against cardiovascular events, reducing acute myocardial infarction events across numerous observational and clinical studies.[47] In cohort studies, influenza vaccination was associated with reductions in all-cause mortality, as well as mortality attributed to a variety of diseases such as stroke, heart disease, pneumonia, chronic obstructive pulmonary disease, diabetes, renal disease, and malignancy.[46] In people with type 2 diabetes, the influenza vaccination was associated with reductions in all-cause mortality and hospital admission rates related to stroke, heart failure, and pneumonia or influenza.[45]

These benefits underscore the need to implement influenza vaccines in clinical practice as a routine standard of care; however, immunization rates remain low. During the 2010-2011 and 2016-2017 influenza seasons, the percentage of persons 18 years of age and older who received an influenza vaccination in the prior 12 months increased from 40.5% to 43.3%.[25] In 2015, influenza vaccination rates increased with age: 33.6% of persons 18 through 49 years of age, 45.4% of persons 50 through 64 years of age, and 65.3% of persons 65 years of age and older reported receiving an influenza vaccination.[25]

CLINICAL STUDIES

The clinical development program of Flublok Quadrivalent vaccine included 2 pivotal trials conducted concurrently to support licensure of the vaccine for active immunization in persons 18 years of age and older.[1]

Study PSC12: Efficacy, Immunogenicity, and Safety of Flublok Quadrivalent Vaccine in Persons 50 Years of Age or Older

Study Design[1,2,4]

Study PSC12 (NCT02285998) was a phase 3-4, randomized, observer-blinded, active-controlled, clinical trial conducted during the 2014-2015 influenza season in which 9003 healthy persons 50 years of age and older (mean age 62.5 years) were randomized to receive Flublok Quadrivalent vaccine or a standard-dose quadrivalent inactivated influenza vaccine (SD-IIV4) as an active control; a total of 8604 participants were included in the efficacy population (Flublok Quadrivalent vaccine [n=4303] and SD-IIV4 [n=4301]). Among randomized subjects, 58% were female, 80% white, 18% black/African-American, 5% were of Hispanic/Latino ethnicity, and 2% other races. A total of 5186 (60%) subjects were between 50 and 64 years of age and 3486 (40%) were 65 years of age or older.

Study Endpoints[1,2,4]

The primary efficacy endpoint was polymerase chain reaction (PCR)-confirmed, protocol-defined, influenza-like illness due to any strain of influenza that occurred 14 days or more after vaccination through the end of the influenza season, approximately 6 months postvaccination. Attack rates and relative vaccine efficacy, defined as 1 – [attack rate (Flublok Quadrivalent vaccine)/attack rate (SD-IIV4)], were calculated for the total efficacy population (n=8604) for the primary efficacy endpoint and for several alternative efficacy endpoints. Epidemiologic data from the CDC for the 2014-2015 influenza season indicated that influenza A (H3N2) viruses predominated and that most influenza A/H3N2 viruses were antigenically dissimilar (mismatched), while A/H1N1 and B viruses were antigenically similar (matched) to vaccine antigens.

Secondary endpoints and additional post hoc analyses examined varying definitions of the primary endpoint, including culture-positive, protocol-defined, influenza-like illness and influenza-like illness as defined by CDC criteria, and determined separate efficacy rates against influenza A and influenza B.

The immunogenicity analysis compared postvaccination-HAI GMT ratios and SCRs for all 4 antigens in Flublok Quadrivalent vaccine compared with the corresponding antigens in SD-IIV4 in all subjects enrolled at the 5 sites participating in the serology subset.[3]

For the safety analyses, self-reports of local and systemic reactogenicity for 7 days after immunization were obtained with the use of phone calls and diary cards. Unsolicited events were captured for 28 days after immunization and serious adverse events were recorded for the duration of subject participation.

Results

Efficacy[1,4]

The primary efficacy endpoint of this study was confirmed in 96 of 4303 Flublok Quadrivalent vaccine recipients and in 138 of 4301 SD-IIV4 recipients, yielding a positive relative vaccine efficacy (rVE) of 30% (**Table 1**). The lower

TABLE 1
Primary endpoint: rVE of Flublok Quadrivalent vaccine vs SD-IIV4 for PCR-confirmed, protocol-defined, influenza-like illness[1]

	Flublok Quadrivalent vaccine (N=4303)		SD-IIV4 (N=4301)			
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)	RR	rVE (95% CI)
All PCR-positive influenza[a]	96	2.2	138	3.2	0.70	30 (10, 47)

n=number of cases; N=number of subjects in treatment group; RR=relative risk (Attack Rate Flublok/Attack Rate SD-IIV4); rVE=[(1-RR) x 100].
[a]Primary analysis: All cases of PCR-confirmed influenza are included. Antigenic characterization and genetic sequencing to determine similarity of isolates to vaccine antigens were not performed.

bound of the 2-sided 95% confidence interval (CI) met the prespecified noninferiority criterion of > -20%. Having met the primary efficacy endpoint of the study, the test for superiority of Flublok Quadrivalent vaccine over SD-IIV4 as a prespecified exploratory analysis was also met by the lower bound of the 2-sided 95% CI > +9%.

In additional analyses, the rVE of 43% for culture-confirmed, protocol-defined, influenza-like illness due to any influenza strain also met the predefined lower bound of 95% CI for both noninferiority (> -20%) and an exploratory evaluation of superiority (> +9%, see **Table 2**).

In summary, Flublok Quadrivalent vaccine provided 30% better protection for the PCR-confirmed, protocol-defined, influenza-like illness due to any influenza virus or subtype. Additionally, Flublok Quadrivalent vaccine provided 43% better protection from culture-confirmed, protocol-defined, influenza-like illness due to any influenza virus or subtype.

***Immunogenicity*[4]**

In this study of persons 50 years of age or older, serum samples were obtained on Day 0 prior to vaccination and on Day 28 after vaccination for HAI titers from 614 subjects enrolled at 5 clinical sites selected to participate in the immunogenicity subset analysis. There was no further selection at the subject level with respect to which subjects would participate in the immunogenicity subset. The immunogenicity analysis included SCRs and GMT ratios for the 4 strains (A/H1N1, A/H3N2, B/Yamagata lineage, B/Victoria lineage) included in the vaccines (**Table 3**). Flublok Quadrivalent vaccine met the seroconversion noninferiority criterion (upper bound of the 2-sided 95% CI around the difference between SD-IIV4 and Flublok Quadrivalent vaccine <10%) compared with SD-IIV4 for 2 of the 4 strains (A/H3N2 and B/Yamagata lineage) included in the vaccine.

The Flublok Quadrivalent vaccine cohort demonstrated robust, postvaccination HAI GMT immune responses and

TABLE 2
Secondary endpoints and additional analyses: rVE of Flublok Quadrivalent vaccine vs SD-IIV4 for PCR-confirmed and culture-confirmed, protocol-defined, influenza-like illness[1]

	Flublok Quadrivalent vaccine (N=4303)		SD-IIV4 (N=4301)			
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)	RR	rVE (95% CI)
All culture-confirmed, protocol-defined, influenza-like illness[a,b]	58	1.3	101	2.3	0.57	43 (21, 59)
All PCR-positive influenza A[b]	73	1.7	114	2.7	0.64	36 (14. 53)
All PCR-positive influenza B[b]	23	0.5	24	0.6	0.96	4 (-72, 46)

n=number of cases; N=number of subjects in treatment group.
[a]Post hoc analyses: All cases of influenza A were A/H3N2. Cases of influenza B were not distinguished by lineage.
[b]Culture of PCR-positive samples was performed in Madin-Darby Canine Kidney cells.

TABLE 3
HAI seroconversion rates with Flublok Quadrivalent vaccine vs SD-IIV4 in persons aged ≥50 years (immunogenicity population)[4]

Antigen	Flublok Quadrivalent vaccine (N=314) N (%)	SD-IIV4 (N=300) N (%)	Difference (95% CI)
A/H1N1	141 (44.9)	147 (49.0)	4.1 (-3.8, 12.0)
A/H3N2	171 (54.5)	130 (43.3)	-11.2 (-19.0, **-3.3**)
B/Yamagata	122 (38.9)	115 (38.3)	-0.6 (-8.2, **7.2**)
B/Victoria	66 (21.0)	103 (34.3)	13.3 (6.3, 20.3)

Figures in **bold** meet CBER criterion for noninferiority.

met the GMT ratio criterion for noninferiority to 3 of the 4 strains (A/H1N1, A/H3N2 and B/Yamagata lineage) covered by the vaccine (**Table 4**). Although Flublok Quadrivalent vaccine did not meet noninferiority, as assessed by GMT ratio for the B/Victoria lineage, the absolute GMT values in each vaccine group were within the limits of sensitivity for which this assay is validated (2-fold dilution).

Safety[1,4]

Both Flublok Quadrivalent vaccine and SD-IIV4 had similar and acceptable safety profiles. There were no notable differences between the vaccines in terms of solicited systemic adverse reactions during the 7 days following vaccination (**Table 5**). Subjects who received Flublok Quadrivalent vaccine experienced less injection site pain and tenderness than those who received SD-IIV4. In contrast, injection site redness was slightly more frequent in Flublok Quadrivalent vaccine recipients compared to SD-IIV4 recipients, but these reactions occurred in fewer than 3% of subjects in each group.

In the 28 days following vaccination, 1 or more unsolicited treatment-emergent adverse events occurred in 13.9% of Flublok Quadrivalent vaccine and 14.1% of SD-IIV4 recipients. The rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

Among study participants, 20 deaths occurred in the 6 months post-vaccination, including 8 individuals who received Flublok Quadrivalent vaccine and 12 who received SD-IIV4. No deaths were considered to be related to study vaccine. Serious adverse events were reported by 145 (3.4%) Flublok Quadrivalent vaccine recipients and 132 (3%) SD-IIV4 recipients. No serious adverse events were considered related to study vaccine.

TABLE 4
HAI GMT responses with Flublok Quadrivalent vaccine vs SD-IIV4 in persons ≥50 years of age or older (immunogenicity population)[4]

Antigen	Visit	Flublok Quadrivalent vaccine (N=314) GMT (95% CI)	SD-IIV4 (N=300) GMT (95% CI)	GMR (95% CI)
A/H1N1	Day 0 Day 28	45 (38, 52) 194 (167, 226)	49 (42, 57) 224 (197, 255)	1.15 (0.95, **1.41**)
A/H3N2	Day 0 Day 28	88 (74, 104) 530 (470, 597)	224 (197, 255) 100 (84, 119)	0.69 (0.58, **0.82**)
B/Yamagata	Day 0 Day 28	17 (15, 20) 56 (49, 64)	18 (16, 21) 58 (51, 66)	1.04 (0.86, **1.24**)
B/Victoria	Day 0 Day 28	14 (12, 15) 30 (26, 34)	15 (13, 16) 44 (39, 50)	1.47 (1.24, 1.77)

Figures in **bold** meet CBER criterion for noninferiority.

TABLE 5
Frequency of solicited local injection site reactions and systemic adverse reactions within 7 days of administration of Flublok Quadrivalent vaccine or SD-IIV4 in persons aged ≥50 years (reactogenicity populations)[1,4,a]

	Flublok Quadrivalent vaccine N=4312			SD-IIV4 N=4327		
Reactogenicity Term	**Any Grade n (%)**	**Grade 3 %**	**Grade 4 %**	**Any Grade n (%)**	**Grade 3 %**	**Grade 4 %**
Subjects with ≥1 injection site reaction[a,b]	1621 (37.6)	<1	<1	1745 (40.4)	<1	<1
Local tenderness	1479 (34.3)	<1	<1	1604 (37.1)	<1	<1
Local pain	813 (18.9)	<1	0	950 (22.0)	<1	<1
Firmness/swelling	143 (3.3)	<1	0	115 (2.7)	<1	0
Redness	122 (2.8)	<1	0	87 (2.0)	<1	0
Subjects with ≥1 systemic reactogenicity event[a,c]	1077 (25.0)	1	<1	1106 (25.6)	1	<1
Headache	549 (12.7)	<1	<1	582 (13.5)	1	<1
Fatigue	526 (12.2)	<1	0	521 (12.1)	<1	<1
Muscle pain	366 (8.5)	<1	<1	378 (8.8)	<1	<1
Joint pain	324 (7.5)	<1	0	346 (8.0)	<1	<1
Nausea	212 (4.9)	<1	0	213 (4.9)	<1	<1
Shivering/chills	204 (4.7)	<1	0	187 (4.3)	<1	<1
Fever[d,e]	19 (0.4)	<1	0	21 (0.5)	<1	0

[a]Reactogenicity populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least 1 nonmissing data point for injection site, systemic, or body temperature reactogenicity categories. For local pain, tenderness, and systemic reactions: Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=required emergency room visit or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small); Grade 2=51 to ≤100 mm (medium); Grade 3=>100 mm (large); Grade 4=necrosis or exfoliative dermatitis.
[b]Denominators for injection site reactions: Flublok Quadrivalent vaccine, n=4307, SD-IIV4, n=4319.
[c]Denominators for systemic reactions: Flublok Quadrivalent vaccine, n=4306, SD-IIV4, n=4318.
[d]Denominators for fever: Flublok Quadrivalent vaccine, n=4262, SD-IIV4, n=4282.
[e]Fever defined as ≥100.4°F (38°C). Grade 1 (≥100.4°F to ≤101.1°F); Grade 2 (101.2°F to ≤102.0°F); Grade 3 (102.1°F to ≤104°F); Grade 4 >104°F.

Study PSC16: Immunogenicity and Safety of Flublok Quadrivalent Vaccine in Persons 18 Through 49 Years of Age

Study Design[1,7]

Study PSC16 (NCT02290509) was a phase 3, randomized, observer-blinded, active-controlled, multicenter, clinical trial conducted during the 2014-2015 influenza season in healthy persons 18 through 49 years of age. A total of 1330 subjects were randomized on a 3:1 basis to receive a single intramuscular dose of either Flublok Quadrivalent vaccine (n=998) or SD-IIV4 (n=332). The majority of subjects were female (65%), white (60%), black/African American (37%), and of non-Hispanic/Latino ethnicity (84%), with a mean age of 33.5 years. Of the total vaccinated population, 1292 subjects (969 Flublok Quadrivalent vaccine and 323 SD-IIV4 recipients, respectively) were evaluable for immune responses.

Study Endpoints[1,7]

The coprimary endpoints of the study were GMT ratios and Day 28 SCRs for each of the 4 antigens contained in Flublok Quadrivalent vaccine compared with SD-IIV4.

Pre-and postvaccination hemagglutination inhibition assays (HAI) were performed on sera obtained prior to and 28 days after administration to measure immunogenicity of a single dose of study vaccine. GMTs and SCRs (defined as either a prevaccination HAI titer of <1:10 and a postvaccination HAI titer of ≥1:40, or a prevaccination HAI titer of ≥1:10 and a minimum 4-fold increase in postvaccination HAI titer at Day 28) for both vaccine cohorts were calculated for each vaccine antigen for a noninferiority analysis. Noninferiority in terms of SCR was considered met if the upper bound of the 2-sided 95% CI for the difference between the SCR in the 2 study groups ($SCR_{SD\text{-}IIV4} - SCR_{Flublok\ Quadrivalent\ vaccine}$), did not exceed 10%. Noninferiority in terms of GMT ratios was considered met if the upper bound of the 2-sided 95% CI for the ratio of the GMTs ($GMT_{SD\text{-}IIV4} / GMT_{Flublok\ Quadrivalent\ vaccine}$) did not exceed 1.5.

Results

Immunogenicity[1,7]

Flublok Quadrivalent vaccine was noninferior to SD-IIV4 for 3 of the 4 antigens (A/H1N1, A/H3N2, and B/Yamagata lineage) in terms of both SCRs and GMT ratios (**Tables 6** and **7**). The HAI response to the B/Victoria lineage antigen was low and uninterpretable in both vaccine groups.

Safety[1,7]

The safety analysis included 1330 subjects 18 through 49 years of age (Flublok Quadrivalent vaccine [N=998] and SD-IIV4 [N=332]). The mean age of participants was 33.5 years. Overall, 65% of subjects were female, 59% white/Caucasian, 37% black/African American, 1.0% Native Hawaiian/Pacific Islander, 0.8% American Indian/Alaskan Native, 0.5% Asian, 16% of non-Hispanic/Latino ethnicity, and 1.4% other racial groups.

The safety profile of Flublok Quadrivalent vaccine, both in terms of local and systemic reactogenicity and of spontaneously reported adverse events, was comparable to that of SD-IIV4. **Table 8** summarizes the incidence of solicited local and systemic adverse reactions reported within 7 days of

TABLE 6
Comparison of day 28 postvaccination GMTs for Flublok Quadrivalent vaccine and SD-IIV4 in persons 18 through 49 years of age (immunogenicity population)[1,a,b]

Antigen	Postvaccination GMT Flublok Quadrivalent vaccine N=969	Postvaccination GMT SD-IIV4 N=323	GMT Ratio SD-IIV4/ Flublok Quadrivalent vaccine [95% CI]
A/H1N1	493	397	0.81 (0.71, 0.92)
A/H3N2	748	377	0.50 (0.44, 0.57)
B/Yamagata	156	134	0.86 (0.74, 0.99)
B/Victoria	43	64	1.49 (1.29, 1.71)

[a]The immunogenicity population included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 within specified windows, and had no major protocol deviations that might affect the immune response. The predefined success criterion for the GMT ratio between SD-IIV4 and Flublok Quadrivalent vaccine was that the upper bound of the 2-sided 95% CI of the GMT ratio, SD-IIV4 divided by Flublok Quadrivalent vaccine at 28 days postvaccination, must not exceed 1.5.
[b]HAI titers were assayed using egg-derived antigens.

TABLE 7
Comparison of Day 28 seroconversion rates for Flublok Quadrivalent vaccine and SD-IIV4 in persons 18 through 49 years of age (immunogenicity population)[1,a,b]

Antigen	SCR (%, 95% CI) Flublok Quadrivalent vaccine N=969	SCR (%, 95% CI) SD-IIV4 N=323	SCR Difference (%) SD-IIV4/Flublok Quadrivalent vaccine [95% CI]
A/H1N1	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)	-3.2 (-9.2, 2.8)
A/H3N2	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)	-15.2 (-21.3, -9.1)
B/Yamagata	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)	0.7 (-5.4, 6.9)
B/Victoria	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)	17.6 (11.4, 23.9)

Seroconversion was defined as a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40 or a prevaccination HAI titer ≥1:10 and a minimum 4-fold rise in postvaccination HAI antibody titers.
[a]The immunogenicity population included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 within specified windows, and had no major protocol deviations that might affect the immune response. The predefined success criterion for the SCR difference between SD-IIV4 and Flublok Quadrivalent vaccine was that the upper bound of the 2-sided 95% CI of the SCR difference (SD-IIV4 minus Flublok Quadrivalent vaccine) at 28 days postvaccination must not exceed 10%.
[b]HAI titers were assayed using egg-derived antigens.

vaccination with Flublok Quadrivalent vaccine or SD-IIV4.

In the 28 days following vaccination, 1 or more unsolicited treatment-emergent adverse events occurred in 10.3% of Flublok Quadrivalent vaccine recipients and 10.5% of SD-IIV4 recipients.

No deaths were reported through 6 months postvaccination. Serious adverse events were reported by 12 subjects (10 [1%] Flublok Quadrivalent vaccine recipients and 2 [0.6%] SD-IIV4 recipients). No serious adverse events were considered to be related to study vaccine.

Clinical Trials Summary

The clinical development program of Flublok Quadrivalent vaccine included 2 pivotal trials conducted concurrently to support licensure of the vaccine for active immunization in persons 18 years of age and older.[1]

The trial in persons 50 years of age and older is a head-to-head comparison of clinical efficacy between 2 quadrivalent seasonal influenza vaccines. Flublok Quadrivalent vaccine met both the primary noninferiority endpoint and a prespecified exploratory endpoint of superiority of reducing the incidence of PCR-confirmed protocol-defined, influenza-like illness compared with SD-IIV4.[1,4] Flublok Quadrivalent vaccine provided 30% better protection from PCR-confirmed, protocol-defined, influenza-like illness due to any influenza virus or subtype.[1,2] Additionally, Flublok Quadrivalent vaccine provided 43% better protection from culture-confirmed, protocol-defined, influenza-like illness due to any influenza virus or subtype.[1,2]

In persons 50 years of age and older, noninferior immunogenicity was demonstrated for Flublok Quadrivalent vaccine for 3 of the 4 antigens (A/H1N1, A/H3N2, and B/Yamagata lineage) by GMT ratios.[4] HAI responses to the B/Victoria lineage were relatively weak for each vaccine and the postvaccination GMTs for the 2 vaccine groups were within the validated range of sensitivity of the HAI assay.[4]

In persons 18 through 49 years of age, Flublok Quadrivalent vaccine demonstrated noninferiority to SD-IIV4, meeting both coprimary endpoints (SCR and GMT ratios) for 3 of 4 influenza strains.[1] As was observed in the companion clinical trial in persons 50 years of age and older, the relative vaccine efficacy of Flublok Quadrivalent vaccine against the circulating influenza B strains was similar to that of SD-IIV4, which may suggest that antibody immune responses for the B strains may not fully explain the protective efficacy of the vaccine.[7] Overall, an acceptable immunogenicity analysis combined with a satisfactory safety profile support licensure of Flublok Quadrivalent vaccine in persons 18 through 49 years of age.[7]

In both trials, safety was largely comparable, although injection site pain and tenderness were less frequent in Flublok Quadrivalent vaccine recipients.[1]

The 50 years of age and older population is at increased risk for influenza disease and its complications, as well as the exacerbating effect that the disease can have on their chronic conditions. Flublok Quadrivalent vaccine provided 30% to 43% better protection from influenza disease in persons 50 years of age and older.

TABLE 8
Frequency of solicited local injection site reactions and systemic adverse reactions within 7 days of administration of Flublok Quadrivalent vaccine or SD-IIV4 in persons 18 through 49 years of age (reactogenicity populations)[7]

	Flublok Quadrivalent vaccine N=996 n (%)			SD-IIV4 N=332 n (%)		
Reactogenicity Term	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Subjects with ≥1 injection site reaction[a,b]	510 (51.2)	11 (1.1)	1 (0.1)	172 (51.8)	5 (1.5)	0
Local tenderness	478 (48.0)	9 (0.9)	0	155 (46.7)	4 (1.2)	0
Local pain	367 (36.8)	9 (0.9)	1 (0.1)	121 (36.4)	3 (0.9)	0
Firmness/swelling	49 (4.9)	0	0	10 (3.0)	0	0
Redness	42 (4.2)	0	0	3 (0.9)	0	0
Subjects with ≥1 systemic reaction[a,c]	339 (34.1)	23 (2.3)	1 (0.1)	119 (35.8)	9 (2.7)	1 (0.3)
Headache	202 (20.3)	13 (1.3)	0	70 (21.1)	6 (1.8)	1 (0.3)
Fatigue	164 (16.5)	5 (0.5)	0	55 (16.6)	4 (1.2)	0
Muscle pain	127 (12.8)	9 (0.9)	0	39 (11.7)	3 (0.9)	0
Joint pain	94 (9.5)	9 (0.9)	0	34 (10.2)	2 (0.6)	0
Nausea	89 (9.0)	6 (0.6)	1 (0.1)	31 (9.3)	4 (1.2)	0
Shivering/chills	69 (6.9)	5 (0.5)	0	20 (6.0)	4 (1.2)	0
Fever[d,e]	15 (1.5)	4 (0.4)	0	2 (0.6)	1 (0.3)	0

NOTE: Data are based on the most severe response reported by subjects. Results ≥1% are reported to nearest whole percent; results >0 but <1% reported as <1%.

[a]Reactogenicity populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had ≥1 nonmissing data point for injection site, systemic, or body temperature reactogenicity categories. For local pain, tenderness, and systemic reactions: Grade 1=no interference with activities; Grade 2=prevented some activities, and headache may have required nonnarcotic pain reliever; Grade 3=prevented most or all normal activities or required prescription medications; Grade 4=required visit to emergency department or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small); Grade 2=51 to ≤100 mm (medium); Grade 3=>100 mm (large); Grade 4=necrosis or exfoliative dermatitis.

[b]Denominators for injection site reactions: Flublok Quadrivalent vaccine n=996, SD-IIV4 n=332.

[c]Denominators for systemic reactions: Flublok Quadrivalent vaccine n=994, SD-IIV4 n=332.

[d]Denominators for fever: Flublok Quadrivalent vaccine n=990, SD-IIV4 n=327.

[e]Fever defined as ≥100.4°F (38°C). Grade 1 (≥100.4°F to ≤101.1°F); Grade 2 (101.2°F to ≤102.0°F); Grade 3 (102.1°F to ≤104°F); Grade 4 >104°F.

Flublok® QUADRIVALENT Influenza Vaccine

Product Reference Sheet	
Trade/Brand Name	Flublok® Quadrivalent (Influenza Vaccine)
Category	80.12 (Vaccines)
Licensure Information[1,3]	Flublok vaccine (trivalent) was licensed in 2013 Flublok Quadrivalent vaccine was licensed in 2016
How Supplied and Physical Properties[1]	Flublok Quadrivalent vaccine is supplied as a single-dose, 0.5-mL prefilled syringe in a 10-syringe carton. Flublok Quadrivalent vaccine is a sterile, clear, colorless solution. Flublok Quadrivalent vaccine contains no egg proteins, formaldehyde, antibiotics, or preservatives. The single-dose, prefilled syringes contain no natural rubber latex.
Storage and Handling[1]	Store Flublok Quadrivalent vaccine refrigerated at between 2°C and 8°C (36°F and 46°F). DO NOT FREEZE. Discard if product has been frozen. Protect syringes from light. Do not use after expiration date shown on the label.
CPT®[a] Code	90682
2017-2018 National Drug Code (NDC)[1b]	42874-0117-01 (0.5-mL syringe); 42874-0117-10 (carton of 10)
2017-2018 Vaccine Pricing[48]	Average Wholesale Price (AWP) = $54.75 per dose
How to Order	Contact Sanofi Pasteur at 1-800-VACCINE (1-800-822-2463) or log onto www.vaccineshoppe.com
Indications and Usage[1]	Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vaccine. Flublok Quadrivalent vaccine is approved for use in persons 18 years of age and older.
Safety Information[1]	The most common local adverse reactions to Flublok Quadrivalent vaccine include tenderness and pain at the injection site. The most common systemic reactions include headache, fatigue, myalgia, and arthralgia. Other adverse reactions may occur. Vaccination with Flublok Quadrivalent vaccine may not protect all individuals.

[a]CPT (Current Procedural Terminology) is a registered trademark of the American Medical Association.
[b]In response to FDA guidelines, Sanofi Pasteur has assigned different NDCs to the unit-of-use (vial or syringe) and the outer carton. We ask that your claims systems recognize all NDCs when NDCs are required.

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Protein Sciences Corporation
Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flublok® Quadrivalent safely and effectively. See full prescribing information for Flublok Quadrivalent.

Flublok Quadrivalent (Influenza Vaccine)
Sterile Solution for Intramuscular Injection
2017-2018 Formula
Initial U.S. Approval: 2013

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

- Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older. (1)

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

For intramuscular (IM) injection only (0.5 mL). (2)

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

A sterile solution for injection supplied in 0.5mL single dose pre-filled syringes. (3)

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

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine. (4, 6.2, 11)

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

- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Flublok Quadrivalent. (5.1)
- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok Quadrivalent should be based on careful consideration of potential benefits and risks. (5.2)

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

- In adults 18 through 49 years of age, the most common (≥10%) injection-site reactions were tenderness (48%) and pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (20%), fatigue (17%), myalgia (13%) and arthralgia (10%). (6.1)
- In adults 50 years of age and older, the most common (≥10%) injection site reactions were tenderness (34%) and pain (19%); the most common (≥10%) solicited systemic adverse reactions were headache (13%) and fatigue (12%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

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

- Pregnancy: Pregnancy outcomes in women exposed to Flublok Quadrivalent during pregnancy are being monitored. Contact: Protein Sciences Corporation by calling 1-888-855-7871. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: March 2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older. (see *Clinical Studies [14]*)

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage

Administer Flublok Quadrivalent as a single 0.5-mL dose.

2.2 Administration

Invert the pre-filled syringe containing Flublok Quadrivalent gently prior to affixing the appropriate size needle for intramuscular 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.

The preferred site for injection is the deltoid muscle. Flublok Quadrivalent should not be mixed in the same syringe with any other vaccine.

3 DOSAGE FORMS AND STRENGTHS

Flublok Quadrivalent is a sterile solution supplied in pre-filled, single-dose syringes, 0.5 mL.

4 CONTRAINDICATIONS

Flublok Quadrivalent is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine (see *Post-marketing Experience [6.2], and Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.2 Guillain Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré Syndrome (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 per 1 million persons vaccinated. If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

5.3 Altered Immunocompetence

If Flublok Quadrivalent is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.

5.4 Limitations of Vaccine Effectiveness

Vaccination with Flublok Quadrivalent may not protect all vaccine recipients.

6 ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reactions were tenderness (48%) and pain (37%) ; the most common (≥10%) solicited systemic adverse reactions were headache (20%), fatigue (17%), myalgia (13%), and arthralgia (10%) (see *Clinical Trials Experience [6.1]*).

In adults 50 years of age and older, the most common (≥10%) injection site reactions were tenderness (34%) and pain (19%); the most common (≥10%) solicited systemic adverse reactions were headache (13%) and fatigue (12%) (see *Clinical Trials Experience [6.1]*).

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

Flublok Quadrivalent

Flublok Quadrivalent has been administered to and safety data collected from 998 adults 18-49 years of age (Study 1) and 4328 adults 50 years of age and older (Study 2).

In Studies 1 and 2, local (injection site) and systemic adverse reactions were solicited with the use of a memory aid for 7 days following vaccination, unsolicited adverse events were collected for ~28 days post-vaccination, and serious adverse events (SAEs) were collected for 6 months post-vaccination via clinic visit or remote contact.

Study 1 included 1330 subjects 18 through 49 years of age for safety analysis, randomized to receive Flublok Quadrivalent (n=998) or a comparator inactivated influenza vaccine (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) (n=332) (see *Clinical Studies [14]*). The mean age of participants was 33.5 years. Overall, 65% of subjects were female, 59% white/Caucasian, 37% black/African American, 1.0% Native Hawaiian/Pacific Islander, 0.8% American Indian/Alaskan Native, 0.5% Asian, 1.4% other racial groups, and 16% of Hispanic/Latino ethnicity. Table 1 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or the comparator vaccine.

Table 1: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator[1] in Adults 18-49 Years of Age, Study 1 (Reactogenicity Populations)[1,2]

	Flublok Quadrivalent N=996 %			Comparator N=332 %		
Reactogenicity Term	Any Grade[6]	Grade 3	Grade 4	Any Grade[6]	Grade 3	Grade 4
Subjects with ≥1 injection site reaction[3, 4]	51	1	0	52	2	0
Local Tenderness	48	1	0	47	1	0
Local Pain	37	1	0	36	1	0
Firmness / Swelling	5	0	0	3	0	0
Redness	4	0	0	1	0	0
Subjects with ≥1 systemic reaction[3,5]	34	2	<1	36	3	<1
Headache	20	1	0	21	2	<1
Fatigue	17	1	0	17	1	0
Muscle Pain	13	1	0	12	1	0
Joint Pain	10	1	0	10	1	0
Nausea	9	1	<1	9	1	0
Shivering / Chills	7	1	0	6	1	0
Fever[6, 7]	2	<1	0	1	<1	0

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

[1] Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine manufactured by GlaxoSmithKline.

[2] Study 1 is registered as NCT02290509 under the National Clinical Trials registry.

[3] Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness and systemic reactions: Grade 1 = No interference with activities. Grade 2 = Prevented some activities, and headache may have required non-narcotic pain reliever. Grade 3 = Prevented most or all normal activities or required prescription medications. Grade 4 = Required visit to ER or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium). Grade 3=>100 mm (large). Grade 4=necrosis or exfoliative dermatitis.

[4] Denominators for injection site reactions: Flublok Quadrivalent n = 996, Comparator n =332.

[5] Denominators for systemic reactions: Flublok Quadrivalent n = 994, Comparator n = 332.

[6] Denominators for fever: Flublok Quadrivalent n = 990, Comparator n = 327.

[7] Fever defined as as ≥100.4°F (38°C). Grade 1 (≥100.4°F to ≤101.1°F); Grade 2 (101.2°F to ≤102.0°F); Grade 3 (102.1°F to ≤104°F). Grade 4 >104°F.

Study 2 included 8672 subjects 50 years of age and older for safety analysis, randomized to receive Flublok Quadrivalent (n=4328) or Comparator (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) as an active control (n=4344) (see *Clinical Studies [14]*). The mean age of participants was 62.7 years. Overall, 58% of subjects were female, 80% white/Caucasian, 18% black/African American, 0.9% American Indian/Alaskan Native, 0.4% Asian, 0.2% Native Hawaiian/Pacific Islander, 0.7% other racial groups, and 5% of Hispanic/Latino ethnicity. Table 2 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or Comparator.

Table 2: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator[1] in Adults 50 Years of Age and Older, Study 2 (Reactogenicity Populations)[2, 3]

	Flublok Quadrivalent N=4312 %			Comparator N=4327 %		
Reactogenicity Term	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Subjects with ≥1 injection site reaction[3, 4]	38	<1	<1	40	<1	<1
Local Tenderness	34	<1	<1	37	<1	<1
Local Pain	19	<1	0	22	<1	<1
Firmness / Swelling	3	<1	0	3	<1	0
Redness	3	<1	0	2	<1	0
Subjects with ≥1 systemic reactogenicity event[3,5]	25	1	<1	26	1	<1
Headache	13	<1	<1	14	1	<1
Fatigue	12	<1	0	12	<1	<1
Muscle Pain	9	<1	<1	9	<1	<1
Joint Pain	8	<1	0	8	<1	<1
Nausea	5	<1	0	5	<1	<1
Shivering / Chills	5	<1	0	4	<1	<1
Fever[6,7]	<1	<1	0	1	<1	0

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.
[1]Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.
[2] Study 2 is registered as NCT02285998 under the National Clinical Trials registry.
[3] Reactogenicity Populations were defined as all randomized subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories. For local pain, tenderness, and systemic reactions: Grade 1=No interference with activity. Grade 2=Some interference with activity. Grade 3=Prevents daily activity. Grade 4=Required ER visit or hospitalization. For injection site redness and firmness/swelling: Grade 1=25 to ≤50 mm (small). Grade 2=51 to ≤100 mm (medium). Grade 3=>100 mm (large). Grade 4=necrosis or exfoliative dermatitis.
[4] Denominators for injection site reactions: Flublok Quadrivalent n = 4307, Comparator n = 4319.
[5] Denominators for systemic reactions: Flublok Quadrivalent n = 4306, Comparator n = 4318.
[6] Denominators for fever: Flublok Quadrivalent n = 4262, Comparator n = 4282.
[7] Fever defined as ≥100.4°F (38°C). Grade 1 (≥100.4°F to ≤101.1°F); Grade 2 (101.2°F to ≤102.0°F); Grade 3 (102.1°F to ≤104°F). Grade 4 >104°F.

Among adults 18-49 years of age (Study 1), through 6 months post-vaccination, no deaths were reported. SAEs were reported by 12 subjects, 10 (1%) Flublok Quadrivalent recipients and 2 (0.6%) Comparator recipients. No SAEs were considered related to study vaccine.

Among adults 50 years of age and older (Study 2), 20 deaths occurred in the 6 months post-vaccination, including 8 Flublok Quadrivalent and 12 Comparator recipients. No deaths were considered related to study vaccine. SAEs were reported by 145 (3.4%) Flublok Quadrivalent recipients and 132 (3%) Comparator recipients. No SAEs were considered related to study vaccine.

In the 28 days following vaccination, one or more unsolicited treatment emergent adverse events occurred in 10.3% of Flublok Quadrivalent and 10.5% of Comparator recipients in Study 1 (adults 18-49 years of age) and in 13.9% of Flublok Quadrivalent and 14.1% of Comparator recipients in Study 2 (adults ≥50 years of age). In both studies, rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

Flublok (Trivalent Formulation)
The safety experience with Flublok is relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions (see *Description [11]*).

Flublok (trivalent formulation) has been administered to and safety data collected from a total of 4547 subjects in five clinical trials (Studies 3-7): 2497 adults 18 through 49 years, 972 adults 50 through 64 years, and 1078 adults 65 years and older. In Studies 3 - 5 and 7, SAEs were collected for 6 months post-vaccination. Study 6 collected SAEs through 30 days following receipt of vaccine. Study 6 also actively solicited pre-specified common hypersensitivity-type reactions through 30 days following receipt of vaccine as a primary endpoint.

Study 3 included 4648 subjects 18 through 49 years of age for safety analysis, randomized to receive Flublok (n=2344) or placebo (n=2304) (2) (see *Clinical Studies [14]*).

Study 4 included 602 subjects 50 through 64 years of age for safety analysis, randomized to receive Flublok (n=300) or another U.S.-licensed trivalent influenza vaccine (Fluzone, manufactured by Sanofi Pasteur, Inc.) as an active control (n=302).

Study 5 included 869 subjects aged 65 years and older for safety analysis, randomized to receive Flublok (n=436) or another U.S.-licensed trivalent influenza vaccine (Fluzone) as an active control (n=433).

Study 6 included 2627 subjects aged 50 years and older for safety analysis, randomized to receive Flublok (n=1314) or another U.S.-licensed trivalent influenza vaccine (Afluria, manufactured by Seqirus Pty Ltd.) as an active control (n=1313). Among subjects 50 through 64 years of age, 672 received Flublok and 665 received Afluria. Among subjects aged 65 years and older, 642 received Flublok and 648 received Afluria.

Study 7 was a Phase 2 dose-finding trial conducted in adults 18 through 49 years of age, 153 of whom received Flublok 135mcg, the licensed trivalent formulation.

Serious Adverse Events
Among 2497 adults 18-49 years of age (Studies 3 and 7 pooled), through 6 months post-vaccination, two deaths were reported, one in a Flublok recipient and one in a placebo recipient. Both deaths occurred more than 28 days following vaccination and neither was considered vaccine-related. SAEs were reported by 32 Flublok recipients and 35 placebo recipients. One SAE (pleuropericarditis) in a Flublok recipient was assessed as possibly related to the vaccine.

Among 972 adults 50-64 years of age (Studies 4 and 6 pooled), through up to 6 months post-vaccination, no deaths occurred, and SAEs were reported by 10 subjects, 6 Flublok recipients and 4 Comparator recipients. One of the SAEs, vasovagal syncope following injection of Flublok, was considered related to administration of study vaccine.

Among 1078 adults 65 years of age and older (Studies 5 and 6 pooled), through up to 6 months post-vaccination, 4 deaths occurred, 2 in Flublok recipients and 2 in Comparator recipients. None were considered related to the study vaccines. SAEs were reported by 80 subjects (37 Flublok recipients, 43 Comparator recipients). None were considered related to the study vaccines.

Among 1314 adults 50 years of age and older (Study 7) for whom the incidence of rash, urticaria, swelling, non-pitting edema, or other potential hypersensitivity reactions were actively solicited for 30 days following vaccination, a total of 2.4% of Flublok recipients and 1.6% of Comparator recipients reported such events over the 30 day follow-up period. A total of 1.9% and 0.9% of Flublok and Comparator recipients, respectively, reported these events in the 7 days following vaccination. Of these solicited events, rash was most frequently reported (Flublok 1.3%, Comparator 0.8%) over the 30 day follow-up period.

6.2 Post-marketing Experience
There is no post-marketing experience with Flublok Quadrivalent.

The following events have been spontaneously reported during post-approval use of Flublok (trivalent formulation). They are described because of the temporal relationship, the biologic plausibility of a causal relationship to Flublok (trivalent formulation), and their potential seriousness. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Immune system disorders: anaphylaxis, anaphylactoid reactions, allergic reactions, and other forms of hypersensitivity.

7 DRUG INTERACTIONS
Data evaluating the concomitant administration of Flublok Quadrivalent with other vaccines are not available.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure
Pregnancy outcomes in women who have been exposed to Flublok Quadrivalent during pregnancy are being monitored. Contact: Protein Sciences Corporation by calling 1-888-855-7871.

Risk Summary
All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Available data on Flublok Quadrivalent and Flublok (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnant women.

There were no developmental studies of Flublok Quadrivalent formulation performed in animals. The developmental effects of Flublok (trivalent formulation) are relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions. A developmental study of Flublok (trivalent formulation) has been performed in rats administered 0.5 mL divided of Flublok (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to Flublok (trivalent formulation) (see *Data [8.1]*).

Clinical Considerations
Disease-associated Maternal and/or Embryo/Fetal Risk
Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data
Animal
In a developmental toxicity study, female rats were administered 0.5 mL divided of Flublok (trivalent formulation) by intramuscular injection twice prior to mating (35 days and 14 days prior to mating) and on gestation Day 6. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation
Risk Summary
It is not known whether Flublok Quadrivalent is excreted in human milk. Data are not available to assess the effects of Flublok (trivalent formulation) or Flublok Quadrivalent 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 Flublok Quadrivalent and any potential adverse effects on the breastfed child from Flublok Quadrivalent or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use
Data from a randomized, controlled trial demonstrated that children 6 months to less than 3 years of age had diminished hemagglutinin inhibition (HI) responses to Flublok (trivalent formulation) as compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that Flublok (trivalent formulation) would not be effective in children younger than 3 years of age (6). Safety and effectiveness of Flublok Quadrivalent have not been established in children 3 years to less than 18 years of age.

8.5 Geriatric Use
Data from an efficacy study (Study 2), which included 1759 subjects ≥65 years and 525 subjects ≥75 years who received Flublok Quadrivalent, are insufficient to determine whether elderly subjects respond differently from younger subjects (see *Clinical Trials Experience [6.1]* and *Clinical Studies [14]*).

11 DESCRIPTION
Flublok Quadrivalent [Quadrivalent Influenza Vaccine] is a sterile, clear, colorless solution of recombinant hemagglutinin (HA) proteins from four influenza viruses for intramuscular injection. It contains purified HA proteins produced in a continuous insect cell line (*expres*SF+®) that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda* (which is related to moths, caterpillars and butterflies), and grown in serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts. Each of the four HAs is expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus), extracted from the cells with Triton X-100 and further purified by column chromatography. The purified HAs are then blended and filled into single-dose syringes.

Flublok Quadrivalent is standardized according to United States Public Health Service (USPHS) requirements. For the 2017-2018 influenza season it is formulated to contain 180 mcg HA per 0.5 mL dose, with 45 mcg HA of each of the following 4 influenza virus strains: A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), B/Brisbane/60/2008, and B/Phuket/3073/2013.

A single 0.5 mL dose of Flublok Quadrivalent contains sodium chloride (4.4 mg), monobasic sodium phosphate (0.195 mcg), dibasic sodium phosphate (1.3 mg), and polysorbate 20 (Tween®20) (27.5 mcg). Each 0.5 mL dose of Flublok Quadrivalent may also contain residual amounts of baculovirus and *Spodoptera frugiperda* cell proteins (≤19 mcg), baculovirus and cellular DNA (≤10 ng), and Triton X-100 (≤100 mcg).

Flublok Quadrivalent contains no egg proteins, antibiotics, or preservatives. The single-dose, pre-filled syringes contain no natural rubber latex.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Flublok Quadrivalent contains recombinant HA proteins of the four strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. These proteins function as antigens which induce a humoral immune response, measured by hemagglutination inhibition (HI) antibody.

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent (usually annual) development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual replacement of one or more influenza virus strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains (i.e., typically two type A and, in quadrivalent formulations, two type B), representing the influenza viruses likely to be circulating in the U.S. in the upcoming winter.

13 NONCLINICAL TOXICOLOGY
Flublok Quadrivalent has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. A developmental toxicity study conducted in rats vaccinated with Flublok (trivalent formulation) revealed no evidence of impaired female fertility (see *Pregnancy [8.1]*).

14 CLINICAL STUDIES
14.1 Efficacy Against Laboratory-Confirmed Influenza
The efficacy of Flublok (trivalent formulation) is relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions (see *Description [11]*).

The efficacy of Flublok (trivalent formulation) in protecting against influenza illness was evaluated in a randomized, observer-blind, placebo-controlled multicenter trial conducted in the U.S. during the 2007-2008 influenza season in adults 18-49 years of age (Study 3) (1).

Study 3 enrolled and vaccinated 4648 healthy adults (mean age 32.5 years) randomized in a 1:1 ratio to receive a single dose of Flublok (n=2344) or saline placebo (n=2304). Among enrolled subjects, 59% were female, 67% were white, 19% African-American, 2% Asian, < 1% other races, and 11% of Latino/Hispanic ethnicity. Culture-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 7 months post-vaccination. ILI was defined as having at least 2 of 3 symptoms (no specified duration) in the following categories: 1) fever ≥100°F; 2) respiratory symptoms (cough, sore throat, or runny nose/stuffy nose); or 3) systemic symptoms (myalgias, arthralgias, headache, chills/sweats, or tiredness/malaise). For subjects with an episode of ILI, nasal and throat swab samples were collected for viral culture.

The primary efficacy endpoint of Study 3 was Centers for Disease Control-defined influenza-like illness (CDC-ILI) with a positive culture for an influenza virus strain antigenically resembling a strain represented in Flublok. CDC-ILI is defined as fever of ≥100°F oral accompanied by cough, sore throat, or both on the same day or on consecutive days. Attack rates and vaccine efficacy (VE), defined as the reduction in the influenza rate for Flublok relative to placebo, were calculated for the total vaccinated cohort (n=4648).

The pre-defined success criterion for the primary efficacy analysis was that the lower bound of the 95% confidence interval (CI) of VE should be at least 40%. Vaccine efficacy against antigenically matched culture-confirmed CDC-ILI could not be determined reliably because 96% of the influenza isolates obtained from subjects in Study 3 were not antigenically matched to the strains represented in the vaccine. An exploratory analysis of VE of Flublok against all strains, regardless of antigenic match, isolated from any subject with an ILI, not necessarily meeting CDC- ILI criteria, demonstrated an efficacy estimate of 44.8% (95% CI 24.4, 60.0). See Table 3 for a presentation of VE by case definition and antigenic similarity.

Table 3: Vaccine Efficacy Against Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age, Study 3*

Case definition	Flublok (trivalent) (N=2344)		Saline Placebo (N=2304)		Flublok Vaccine Efficacy[1], %	95% Confidence Interval
	Cases, n	Rate, %	Cases, n	Rate, %		
Positive culture with a strain represented in the vaccine						
CDC-ILI, all matched strains[2,3]	1	0.04	4	0.2	75.4	(-148.0, 99.5)
Any ILI, all matched strains[4,5]	2	0.1	6	0.3	67.2	(-83.2, 96.8)
Positive culture with any strain, regardless of match to the vaccine						
CDC-ILI, all strains[2,6]	44	1.9	78	3.4	44.6	(18.8, 62.6)
Sub-Type A	26	1.1	56	2.4	54.4	(26.1, 72.5)
Type B	18	0.8	23	1.0	23.1	(-49.0, 60.9)
Any ILI, all strains[4]	64	2.7	114	4.9	44.8	(24.4, 60.0)
Sub-Type A	41	1.7	79	3.4	49.0	(24.7, 65.9)
Type B	23	1.0	36	1.6	37.2	(-8.9, 64.5)

*In Study 3 (NCT00539981) vaccine efficacy analyses were conducted on the Total Vaccinated Cohort (all randomized subjects who received study vaccine according to the treatment actually received and who provided data). Vaccine efficacy (VE) = 1 minus the ratio of Flublok/placebo infection rates (1).
[1] Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987.
[2] Meets CDC influenza-like illness (CDC-ILI) defined as fever of ≥100°F oral accompanied by cough and/or sore throat, on the same day or on consecutive days.
[3] Primary endpoint of trial.
[4] All culture-confirmed cases are considered, regardless of whether they qualified as CDC-ILI.
[5] Secondary endpoint of trial.
[6] Exploratory (prespecified) endpoint of trial.

Study 2 evaluated the efficacy of Flublok Quadrivalent in a randomized, observer-blind, active-controlled, multi-center trial conducted during the 2014-2015 influenza season in adults 50 years of age and older. A total of 8963 healthy, medically stable adults (mean age 62.5 years) were randomized in a 1:1 ratio to receive a single dose of Flublok Quadrivalent (n=4474) or a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator, Fluarix Quadrivalent, manufactured by Glaxo SmithKline) (n=4489). Among randomized subjects, 58% were female, 80% white, 18% black/African-American, 2% other races, and 5% of Hispanic/Latino ethnicity. A total of 5186 (60%) subjects were 50-64 years of age and 3486 (40%) were ≥65 years of age. Real-time polymerase chain reaction (rtPCR) -confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 6 months post- vaccination. ILI was defined as having at least one symptom (no specified duration) in each of two categories of respiratory and systemic symptoms. Respiratory symptoms included sore throat, cough, sputum production, wheezing and difficulty breathing. Systemic symptoms included fever > 99°F (>37°C) oral, chills, fatigue, headache and myalgia. For subjects with an episode of ILI, a nasopharyngeal swab sample was collected for rtPCR testing and reflex viral culture of rtPCR-positive samples.

The primary efficacy endpoint of Study 2 was rtPCR-positive, protocol-defined ILI due to any strain of influenza. Attack rates and relative vaccine efficacy (rVE), defined as 1 – [Attack rate Flublok Quadrivalent/ Attack Rate Comparator], were calculated for the total efficacy population (n=8604) for the primary efficacy endpoint and for several alternative efficacy endpoints (Table 4). Antigenic and phylogenetic evaluations of the similarity ("matching") of clinical isolates to vaccine antigens were not performed. CDC epidemiological data for the 2014-2015 influenza season indicated that Influenza A (H3N2) viruses predominated and that most influenza A/H3N2 viruses were antigenically dissimilar while A/H1N1 and B viruses were antigenically similar to vaccine antigens.

Table 4: Relative Vaccine Efficacy (rVE) of Flublok Quadrivalent versus Comparator against Laboratory-Confirmed Influenza, Regardless of Antigenic Similarity to Vaccine Antigens, Adults 50 Years of Age and Older, Study 2 (Efficacy Population)[1,2]

	Flublok Quadrivalent (N=4303)		Comparator (N=4301)		RR	rVE % (95% CI)
	n	Attack Rate % (n/N)	n	Attack Rate % (n/N)		
All rtPCR-positive Influenza[3]	96	2.2	138	3.2	0.70	30 (10, 47)
All rtPCR-positive Influenza A[4]	73	1.7	114	2.7	0.64	36 (14, 53)
All rtPCR-positive Influenza B[4]	23	0.5	24	0.6	0.96	4 (-72, 46)
All Culture-confirmed Protocol-defined ILI[4,5]	58	1.3	101	2.3	0.57	43 (21, 59)

Abbreviations: rtPCR=reverse transcriptase polymerase chain reaction; Comparator=U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline; n=number of influenza cases; N=number of subjects in treatment group; RR=relative risk (Attack Rate Flublok/Attack Rate IIV4); rVE = [(1-RR) x 100].

[1]Study 2 is registered as NCT02285998.

[2]Efficacy Population included all randomized subjects who received study vaccine and provided any follow-up documentation for influenza-like illness beginning at least 14 days postvaccination. Excluded subjects with protocol deviations that could adversely affect efficacy.

[3]Primary Analysis. All cases of rtPCR-confirmed influenza are included. Antigenic characterization and genetic sequencing to determine similarity of isolates to vaccine antigens were not performed. CDC surveillance data indicated that the majority of influenza A/H3N2 wild type viruses were antigenically distinct whereas influenza A/H1N1 and type B viruses were antigenically similar to vaccine antigens during the 2014-2015 season. Study 2 met the pre-specified success criterion for the primary endpoint (lower limit of the 2-sided 95% CI of vaccine efficacy for Flublok Quadrivalent relative to Comparator should be not less than -20%).

[4] *Post hoc* analyses. All cases of influenza A were A/H3N2. Cases of influenza B were not distinguished by lineage.

[5] Culture of rtPCR-positive samples was performed in MDCK cells.

14.2 Immunogenicity of Flublok Quadrivalent

Study 1 evaluated the immunogenicity of Flublok Quadrivalent as compared to a U.S.-licensed quadrivalent inactivated influenza vaccine (Comparator) (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) in a randomized, observer-blind, active-controlled, multi-center trial conducted during the 2014-2015 influenza season in healthy adults 18-49 years of age. A total of 1350 subjects were enrolled, randomized 3:1, and vaccinated with Flublok Quadrivalent (998 subjects) or Comparator (332 subjects). Subjects were predominantly female (65%), white (60%), black/African American (37%), and of non-Hispanic/Latino ethnicity (84%), with a mean age of 33.5 years. Of the total vaccinated population, 1292 subjects (969 Flublok Quadrivalent and 323 IIV4 recipients, respectively) were evaluable for immune responses (Immunogenicity Population).

Post-vaccination immunogenicity was evaluated on sera obtained 28 days after administration of a single dose of study vaccine. Hemagglutination inhibition (HI) geometric mean titers (GMTs) were determined for the two vaccine groups for each vaccine antigen. Immunogenicity was compared by calculating the difference in seroconversion rates (SCR) and the ratios of GMTs of Comparator to Flublok Quadrivalent. Seroconversion was defined as either a pre-vaccination HI titer of <1:10 and a postvaccination HI titer of $\geq$1:40, or a pre-vaccination HI titer of $\geq$1:10 and a minimum 4-fold rise in postvaccination HI titer, at Day 28.

Study 1 had eight co-primary endpoints: Day 28 HI seroconversion rates and GMTs for each of the four antigens contained in the study vaccines. GMTs were compared based on the upper bound of the two-sided 95% CI of the GMT ratio of Comparator to Flublok Quadrivalent. Success in meeting this endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of $GMT_{Comparator}$ / $GMT_{Flublok\ Quadrivalent}$ $\leq$1.5 (7). Flublok Quadrivalent met the success criterion for GMTs for three of the four antigens but not for the B/Victoria lineage antigen (Table 5).

Table 5: Comparison of Day 28 Post-Vaccination Geometric Mean Titers (GMT) for Flublok Quadrivalent and Comparator in Adults 18-49 Years of Age, Study 1 (Immunogenicity Population) [1,2,3,4]

Antigen	Post-vaccination GMT Flublok Quadrivalent N=969	Post-vaccination GMT Comparator N=323	GMT Ratio Comparator/ Flublok Quadrivalent [95% CI]
A/H1N1	493	397	0.81 (0.71, 0.92)
A/H3N2	748	377	0.50 (0.44, 0.57)
B/Yamagata	156	134	0.86 (0.74, 0.99)
B/Victoria	43	64	1.49 (1.29, 1.71)

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

[1] Study 1 is registered as NCT02290509.

[2] The Immunogenicity Population included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 within specified windows, and had no major protocol deviations that might adversely affect the immune response. The pre-defined success criterion for the GMT ratio of Comparator to Flublok Quadrivalent was that the upper bound of the 2-sided 95% CI of the GMT ratio, $GMT_{Comparator}$ / $GMT_{Flublok\ Quadrivalent}$ at 28 days post-vaccination, must not exceed 1.5 (7).

[3] HI titers were assayed using egg-derived antigens.

[4] Comparator: U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

Success in meeting the seroconversion rate (SCR) endpoint was pre-defined as an upper bound (UB) of the two-sided 95% CI of $SCR_{Comparator} - SCR_{Flublok\ Quadrivalent}$ $\leq$10%. Flublok Quadrivalent met the success criterion for SCRs for three of the four antigens but not for the B/Victoria lineage antigen (Table 6). Sub-population analyses of immunogenicity did not reveal significant differences between genders. Sub-analyses according to race and ethnicity were not informative because the sizes of the subsets were insufficient to reach meaningful conclusions. The HI response to the B/Victoria lineage antigen was low in both vaccine groups.

Table 6: Comparison of Day 28 Seroconversion Rates for Flublok Quadrivalent and Comparator in Adults 18-49 Years of Age, Study 1 (Immunogenicity Population) [1,2,3,4]

Antigen	SCR (%, 95% CI) Flublok Quadrivalent N=969	SCR (%, 95% CI) Comparator N=323	SCR Difference (%) Comparator - Flublok Quadrivalent [95% CI]
A/H1N1	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)	-3.2 (-9.2, 2.8)
A/H3N2	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)	-15.2 (-21.3, -9.1)
B/Yamagata	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)	0.7 (-5.4, 6.9)
B/Victoria	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)	17.6 (11.4, 23.9)

Abbreviations: CI, confidence interval; SCR, seroconversion rate

Seroconversion was defined as a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer $\geq$1:40 or a pre-vaccination HI titer $\geq$1:10 and a minimum four-fold rise in post-vaccination HI antibody titer.

[1]Study 1 is registered as NCT02290509.

[2] The Immunogenicity Population included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 within specified windows, and had no major protocol deviations that might adversely affect the immune response. The pre-defined success criterion for the SCR difference between Comparator and Flublok Quadrivalent was that the upper bound of the 2-sided 95% CI of the SCR difference IIV4 – Flublok Quadrivalent at 28 days post-vaccination, must not exceed 10%. (7)

[3] HI titers were assayed using egg-derived antigens.

[4] Comparator was a U.S.-licensed quadrivalent inactivated influenza vaccine, Fluarix Quadrivalent, manufactured by GlaxoSmithKline.

15 REFERENCES

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3. **Baxter R, Patriarca PA, Ensor K, et al.** Evaluation of the safety, reactogenicity and immunogenicity of FluBlok trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. *Vaccine*. 2011, Vol. 29, pp. 2272-2278.

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5. **Izikson R, Laffell D, Bock A, et. al.** Comparison of the Safety of Flublok® versus Licensed Inactivated Influenza Vaccine in Healthy, Medically Stable Adults $\geq$50 Years of Age. *Vaccine*. In press.

6. **King JC, Cox MMJ, Reisinger K, et. al.** Evaluation of the safety, reactogenicity and immunogenicity of FluBlok trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy children aged 6-59 months. *Vaccine*. 2009, Vol. 27, pp. 6589-6594.

7. **CBER/FDA**. *Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*. s.l. : DHHS/CBER/FDA, 2007.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Flublok Quadrivalent is supplied as a single-dose, 0.5 mL syringe in a 5 or 10 syringe carton:

Presentation	Carton NDC Number	Components and NDC Number
Single-Dose Pre-filled Syringe	42874-117-10	Ten 0.5 mL single-dose pre-filled syringes [NDC 42874-117-01]

16.2 Storage and Handling

- Store refrigerated between 2° and 8°C (36° and 46°F).
- Do not freeze. Discard if product has been frozen.
- Protect syringes from light.
- Do not use after expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION

Inform the vaccine recipient of the potential benefits and risks of vaccination with Flublok Quadrivalent.

Inform the vaccine recipient that:

- Flublok Quadrivalent contains non-infectious proteins that cannot cause influenza.
- Flublok Quadrivalent stimulates the immune system to produce antibodies that help protect against the influenza viruses carrying the proteins contained in the vaccine, but does not prevent other respiratory infections.

Instruct the vaccine recipient to report any adverse events to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS).

Provide the vaccine recipient with the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to vaccination. These materials are available free of charge at the Centers for Disease Control (CDC) website (www.cdc.gov/vaccines).

Encourage women who receive Flublok or Flublok Quadrivalent while pregnant to notify Protein Sciences by calling 1-888-855-7871.

Instruct the vaccine recipient that annual vaccination to prevent influenza is recommended.

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