



**FLUAD™ (Influenza Vaccine, Adjuvanted):**  
**An Influenza Vaccine Targeting**  
**the 65+ Population**

# **Product Monograph**



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## EXECUTIVE SUMMARY

### Epidemiology and Pathogenesis of Influenza

- Antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation since 1977.<sup>1</sup>
- Although the epidemiology of influenza strains can vary dramatically from year to year and region to region, on average, influenza A has been the predominant circulating influenza strain in the United States (70%-99% from 2009-2013).<sup>2-5</sup>
  - A/H3N2 strains have accounted for the majority of influenza A infections<sup>a</sup> and are by far the most common cause of influenza-related hospitalization and death in the elderly.<sup>2-7</sup>
  - An estimated 85% of the total influenza-associated respiratory and circulatory deaths in the elderly in the United States from 1990 to 1999 were attributed to influenza A; A/H3N2 strains accounted for 80.5% of deaths.<sup>7</sup>

### The Burden of Influenza Illness for Adults Aged 65 Years and Older

- Influenza, pneumonia, and related cardiovascular complications are among the 6 leading causes of catastrophic disability in the elderly.<sup>6</sup>
- An estimated 50% to 60% of hospitalizations and 90% of deaths related to influenza occur in people aged 65 years and older.<sup>8</sup>
- During the winter season, influenza is the main cause of increased mortality in patients with underlying chronic comorbid conditions, such as acute ischemic heart disease, stroke, and pneumonia.<sup>9</sup>

<sup>a</sup>Except for the 2009-2010 season when the pandemic H1N1 strain predominated.<sup>3</sup>

## Adults Aged 65 Years and Older Present Unique Challenges for Influenza Prevention

- Adults older than 65 years experience worse outcomes in response to influenza infection in part because of age-related weakening of their immune systems, or immunosenescence.<sup>6,10</sup> Older adults also experience impaired long-term immune responses to vaccination in general, resulting in a shorter duration of immunological protection.<sup>10</sup>
- In an effort to reduce the severe outcomes of influenza, such as hospitalizations and deaths, annual vaccination is recommended for people who have an elevated risk for such outcomes including those aged 65 years and older.<sup>11</sup>

## Overview of FLUAD

- FLUAD is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD is approved for use in persons 65 years of age and older. Approval is based on the immune response elicited by FLUAD. Data demonstrating a decrease in influenza disease after vaccination with FLUAD are not available.<sup>1</sup>
- Noninferiority of FLUAD in relation to AGRIFLU (influenza vaccine) was established for all 3 vaccine strains on the basis of both seroconversion rates and geometric mean titers (GMTs).<sup>1</sup>
- In clinical trials, the safety profile of FLUAD was generally similar to that of conventional nonadjuvanted comparators. While higher rates of solicited adverse reactions were noted, they were typically mild to moderate in severity.<sup>1,12</sup>
- FLUAD is a sterile suspension for intramuscular injection supplied in 0.5-mL single-dose prefilled syringes.<sup>1</sup>
- FLUAD is approved in over 30 countries; and to date, more than 81 million FLUAD doses have been distributed worldwide.<sup>13</sup>

# EPIDEMIOLOGY AND PATHOGENESIS OF INFLUENZA

## Epidemiology of influenza strains

Influenza refers to an acute contagious respiratory illness that affects the upper and/or lower respiratory tract and is caused by influenza viruses.<sup>14,15</sup> Antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation since 1977.<sup>1</sup> Although the epidemiology of influenza strains can vary dramatically from year to year and region to region, on average, influenza A has been the predominant circulating influenza strain in the United States (70%-99% from 2009-2013). In particular, A/H3N2 strains have accounted for the majority of influenza A infections (except for the 2009-2010 season when the pandemic H1N1 strain predominated) and are by far the most common cause of influenza-related hospitalization and death in the elderly.<sup>2-7</sup> An estimated 85% of the total influenza-associated respiratory and circulatory deaths in the elderly in the United States from 1990 to 1999 were attributed to influenza A; A/H3N2 strains accounted for 80.5% of deaths.<sup>7</sup>

## Influenza disease pathogenesis

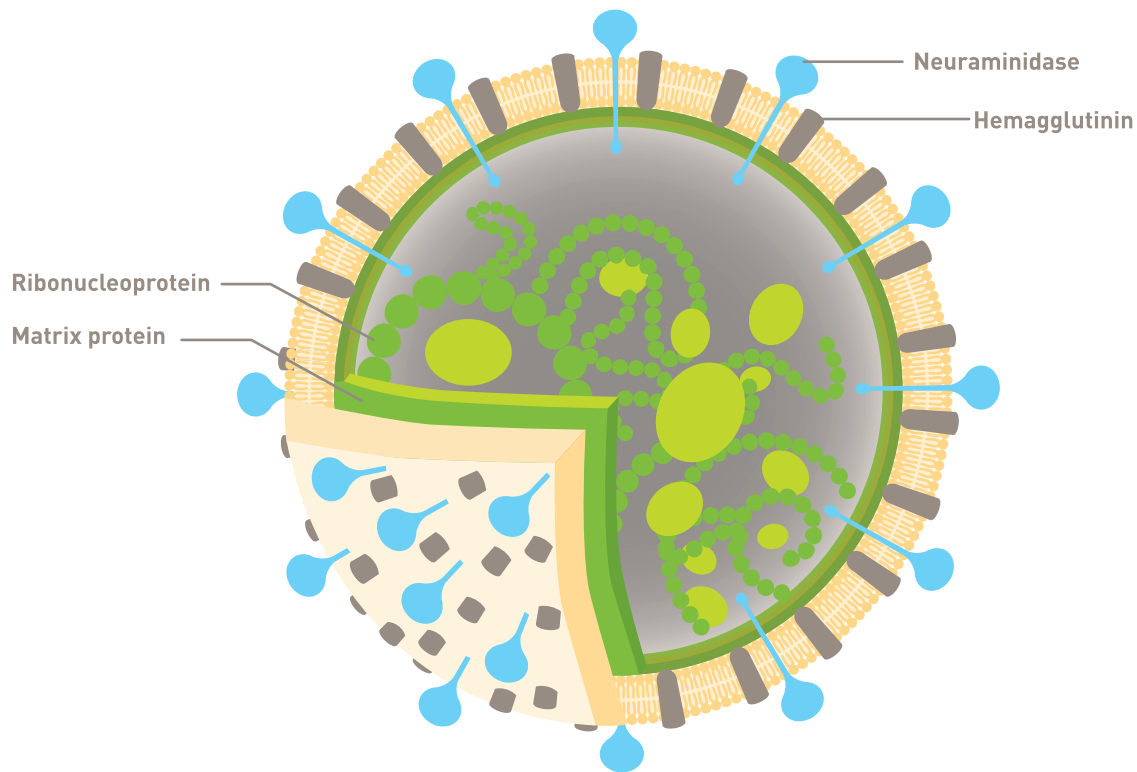
### *Transmission*

Influenza virus is most likely transmitted through aerosolized airway secretions released by coughing and sneezing of acutely infected individuals; however, transmission by hand-to-hand contact, other personal contact, and fomites is also possible.<sup>14,16</sup>

Once the virus gains access to the airway and infects respiratory tract cells, it replicates within 4 to 6 hours.<sup>14,16</sup> It is then released to infect neighboring cells, allowing the infection to spread to a large number of cells over several hours.<sup>14</sup> The incubation time depends on the amount of virus the individual is first exposed to but can range between 18 and 72 hours.<sup>14</sup> Viral shedding may begin 24 hours before the onset of symptoms, reaching a maximum for 24 to 48 hours, followed by a sudden decrease in viral concentration.<sup>16</sup> Typically, influenza virus is no longer detectable after 5 to 10 days of viral shedding.<sup>16</sup> Shedding often takes longer in young children and in people who are immunocompromised.<sup>16</sup>

### *Antigenic drift*

All 3 different genera of influenza viruses, influenza types A, B, and C, belong to the orthomyxoviridae family.<sup>14</sup> These virus types are designated based on nucleoprotein and matrix antigen characteristics. Influenza A viruses are further subtyped by hemagglutinin and neuraminidase surface antigens (**Figure 1**).<sup>14</sup> Because both of these antigens on the influenza A viral surface are highly prone to undergoing selective mutation, or antigenic drift, the annual influenza vaccine formulation may need to be updated every year.<sup>14,17</sup> A high rate of antigenic drift also explains why influenza type A is responsible for the most severe and extensive influenza outbreaks.<sup>14,17</sup> Although influenza types B and C have similar designations, they are not classified by hemagglutinin and neuraminidase subtypes. This is because intratypic variations are less frequent in influenza B and are possibly nonexistent in influenza C surface antigens.<sup>14</sup> As such, the less frequent variations in influenza type B surface antigens may account for the lower disease severity associated with this strain.<sup>14</sup> Similarly, influenza C virus is an infrequent cause of disease in humans.<sup>14</sup>



**Figure 1.** Schematic view of influenza virus.<sup>18</sup>

## Signs and symptoms of influenza disease

Influenza disease is often characterized by a sudden onset of systemic symptoms that may include headache, fever, extreme exhaustion, muscle pain, and malaise.<sup>14,16,19</sup> Those infected with the influenza virus may present with symptoms of varying severity, ranging from a mild respiratory disease similar to the common cold to severe exhaustion with few respiratory symptoms. Fever can range from 100.4°F to 105.8°F (38°C–41°C). It usually peaks within 24 hours of disease onset and gradually decreases over 2 to 3 days; however, fever may last for up to a week.<sup>14</sup> Most often, respiratory symptoms are noticed once systemic symptoms diminish and include sore throat or persistent cough that can last for more than a week.<sup>14</sup>

Presentation of influenza disease may be subtle in the elderly in whom general symptoms (eg, anorexia, malaise, weakness, dizziness) predominate, yet common symptoms (eg, sore throat, fever, muscle pain) may be absent.<sup>14</sup> Older adults may also experience profuse sweating and mottled extremities.<sup>14</sup>

## Prevention of influenza

Vaccination is the most important measure available to help prevent influenza.<sup>20,21</sup> Currently, 2 types of influenza vaccines are available: inactivated and live attenuated.<sup>16</sup> Inactivated influenza vaccines, colloquially known as a flu shot, can contain killed virus, whole viral particles, or hemagglutinin fragments.<sup>18</sup> Live attenuated influenza vaccines are available as an intranasal spray and contain a live but weakened version of the virus that cannot cause influenza disease.<sup>14,22</sup>

Influenza vaccines are also available as trivalent or quadrivalent formulations. Trivalent vaccines contain 2 subtypes of influenza A (H3N2 and H1N1) and 1 strain of influenza B. Quadrivalent vaccines,

on the other hand, have an additional influenza B lineage.<sup>14</sup> In the United States, inactivated influenza vaccines are mostly available as a quadrivalent formulation, with some trivalent formulations still available. The live attenuated vaccine is only available as a quadrivalent formulation.<sup>14,16</sup>

Influenza vaccine efficacy is variable and depends on multiple factors including matching vaccine composition to predicted circulating variants before the start of the flu season and on the body's immune function.<sup>10,18</sup>

## THE BURDEN OF INFLUENZA ILLNESS FOR ADULTS AGED 65 YEARS AND OLDER

Adults aged 65 years and older are particularly vulnerable to influenza and have a high risk of experiencing influenza-related complications such as bacterial pneumonia, heart attack, and stroke.<sup>8,23,24</sup>

### Morbidity and mortality associated with influenza in the 65+ population

Influenza, pneumonia, and related cardiovascular complications are among the 6 leading causes of catastrophic disability in the elderly.<sup>6</sup> In fact, this population accounts for most seasonal influenza-related hospitalizations and deaths.<sup>7,25</sup> An estimated 50% to 60% of hospitalizations and 90% of deaths related to influenza occur in people aged 65 years and older.<sup>8</sup> Furthermore, influenza-related hospitalization and bed rest can result in a significant loss of lower limb muscle strength with a devastating impact on the elderly including long-lasting diminished quality of life, loss of independence in activities of daily living, and functional decline.<sup>6</sup>

Influenza is the main cause of **INCREASED MORTALITY** in patients with underlying chronic comorbid conditions such as

**ACUTE ISCHEMIC HEART DISEASE, STROKE, AND PNEUMONIA\***

### The public health burden of influenza in the 65+ population

Illness and mortality from influenza in the elderly account for considerable health care costs and workplace productivity losses, underscoring the medical and economic need to prevent influenza in this population.<sup>26</sup>

As shown in **Figure 2**, adults aged 65 years and older account for the highest amount of influenza-related outpatient visits, hospitalization days, days of productivity lost, and life-years lost.<sup>26</sup>

This population also accounts for approximately 64% of the total economic burden of influenza in the United States.<sup>26</sup>

**\$ IN 2003**  
THE TOTAL **ECONOMIC**  
BURDEN OF INFLUENZA WAS

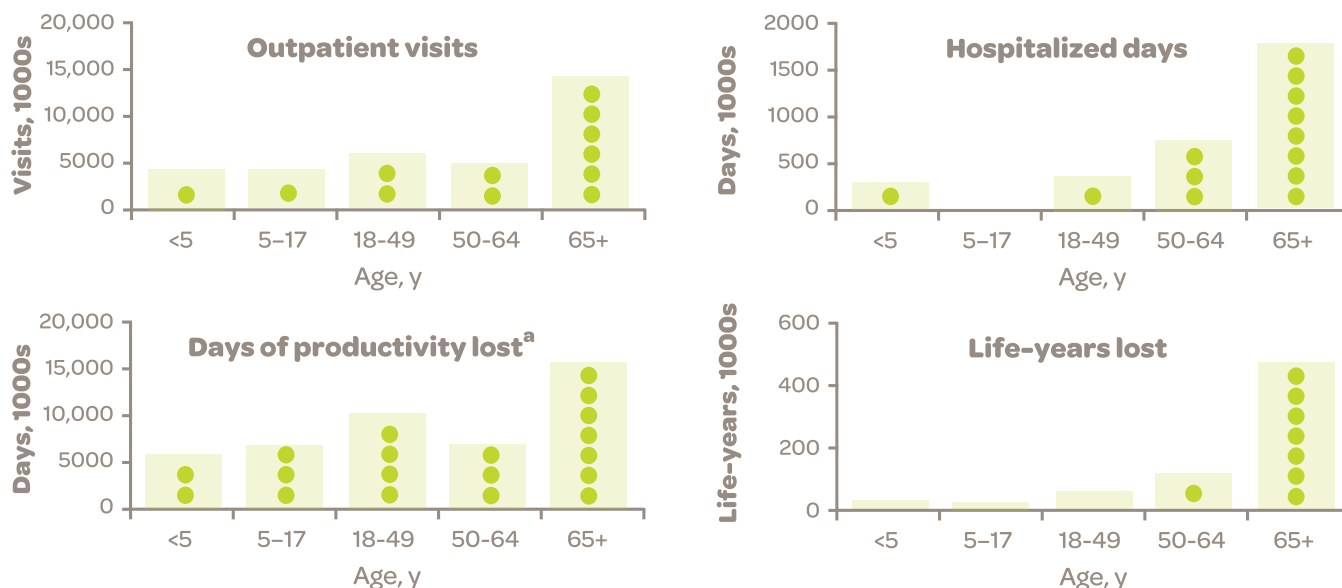


**\$87.1**  
**BILLION**



OF WHICH **~64%**  
WAS BORNE BY ADULTS AGED  
**65 YEARS AND OLDER**<sup>26</sup>





**Figure 2.** Annual burden of influenza in the United States by age group and health outcome in thousands.<sup>26</sup>

## ADULTS AGED 65 YEARS AND OLDER PRESENT UNIQUE CHALLENGES FOR INFLUENZA PREVENTION

### Age-related changes in immune function

When compared with younger adults, adults older than 65 years often experience worse outcomes in response to influenza infection in part because of age-related weakening of their immune systems, or immunosenescence.<sup>6,10</sup> Reduced functionality of certain immune cells and reduced ability to present antigens for initiation of further immune responses result in a decreased level of antigen taken up by cells of the immune system at the site of injection.<sup>10</sup> Older adults also often experience impaired long-term immune responses to vaccination in general, resulting in a shorter duration of immunological protection.<sup>10</sup> In an effort to reduce the severe outcomes of influenza, such as hospitalizations and deaths, annual vaccination is recommended for people who have an elevated risk for such outcomes including those aged 65 years and older.<sup>11</sup>

## Strategies to improve vaccine-mediated protection in the elderly

Several strategies have been developed in an effort to overcome those limitations and improve vaccine-mediated protection for the elderly. These include high-dose vaccines, alternative routes of administration, and adjuvanted vaccines.<sup>28</sup>

The high-dose influenza vaccine contains 4 times the antigen compared with standard influenza vaccines to trigger a stronger immune response.<sup>28</sup> Alternative routes of administration for adults aged 65 years and older include intradermal routes that trigger localized immunity upon pathogen entry.<sup>28</sup> FLUAD™ (influenza vaccine, adjuvanted) contains the proprietary adjuvant MF59® that is thought to generate a strong immune response to influenza vaccination by increasing the recruitment of immune cells to the injection site and improving the antigen presentation process.<sup>28</sup>

### Immune potentiation with the adjuvant MF59

Aluminum-based adjuvants have been in the market since the early 20th century.<sup>29</sup> However, no other novel adjuvants had been approved until 1997, when MF59 was included in a licensed influenza vaccine for the elderly (FLUAD) in Italy.<sup>29,30</sup>

MF59 is an oil-in-water emulsion, a formulation that was critical in the development of a successful adjuvanted vaccine against influenza.<sup>30</sup> By lowering oil content, oil-in-water emulsions significantly improve the tolerability profile and ease of use compared to that previously seen with water-in-oil emulsions.<sup>29,30</sup> Squalene, the oil component in MF59, is a natural substance derived from the liver and is a metabolic intermediate in the synthesis of cholesterol and steroid hormones.<sup>30,31</sup>

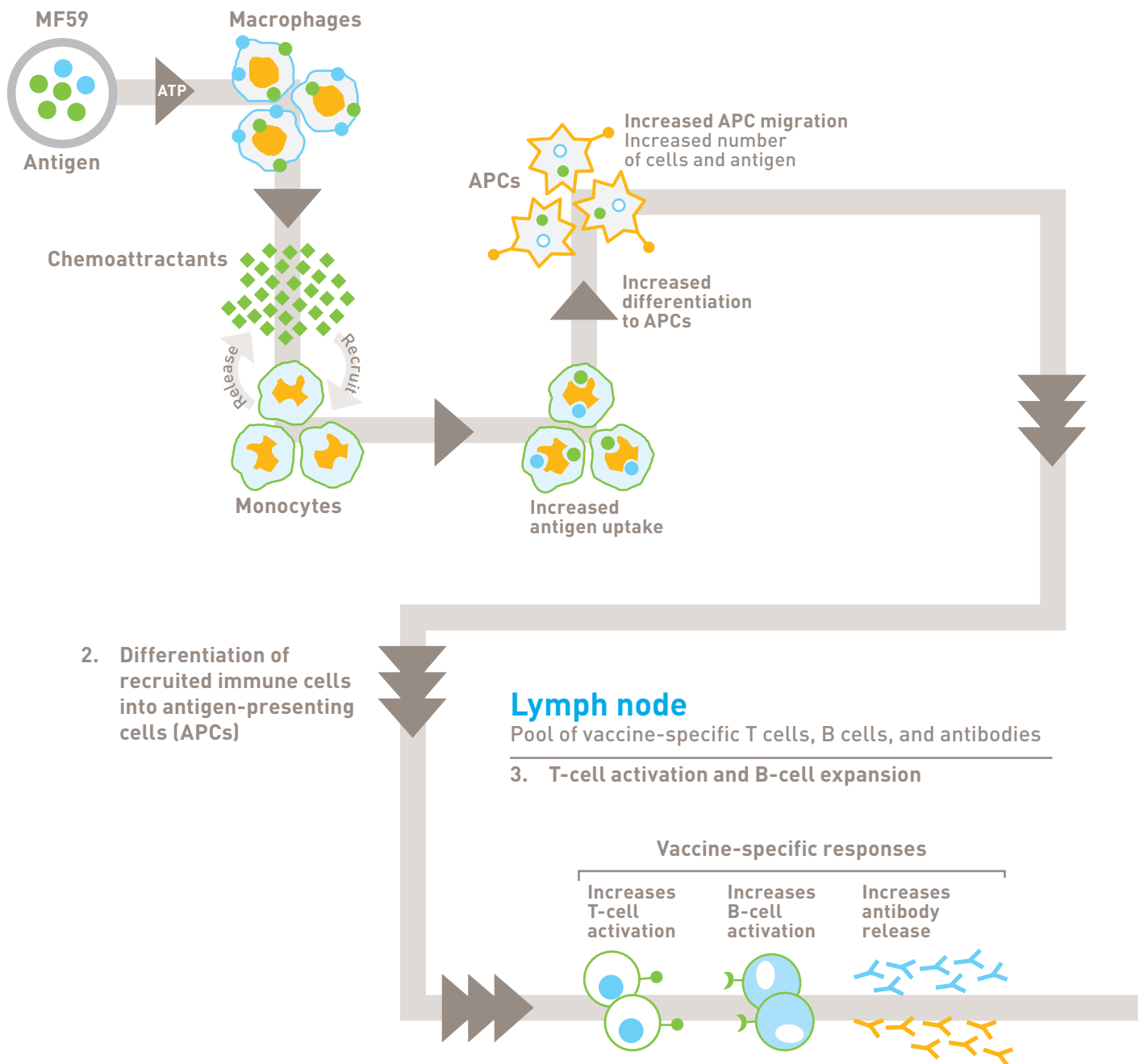
Studies in both in vitro human immune cells and in vivo mouse immunization modules suggest that MF59 recruits immune cells to the injection site and enhances their uptake of antigen.<sup>30</sup> Furthermore, studies with avian H5N1 influenza virus strains suggest that MF59 also has the potential to increase influenza epitope recognition and broaden cross-clade neutralization.<sup>32,33</sup>

MF59's proposed mechanism of action is depicted in **Figure 3**. Studies suggest that intramuscular injection of an MF59-adjuvant vaccine first leads to recruitment of immune cells at the site of injection. These cells, including monocytes, macrophages, dendritic cells, and neutrophils, respond by signaling further recruitment of phagocytic cells.<sup>29,30</sup> It is hypothesized that MF59 then induces differentiation of recruited immune cells into antigen-presenting cells. Because signal amplification results in an increased influx of immune cells, there is a more efficient transport of antigen to the lymph nodes.<sup>29</sup> Once in the lymph nodes, antigen presentation leads to activation and expansion of T and B cells and to antibody production.<sup>29</sup>

## Injection site (IM)

Local immune activation loop

### 1. MF59 recruits immune cells



**The mechanism of action of MF59 is not fully understood.**

**Figure 3.** Proposed mechanism of action of MF59.<sup>29</sup>

## OVERVIEW OF FLUAD






### Indications and usage

FLUAD is an inactivated influenza virus vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD is approved for use in persons 65 years of age and older. Approval is based on the immune response elicited by FLUAD. Data demonstrating a decrease in influenza disease after vaccination with FLUAD are not available.<sup>1</sup>

### Contraindications

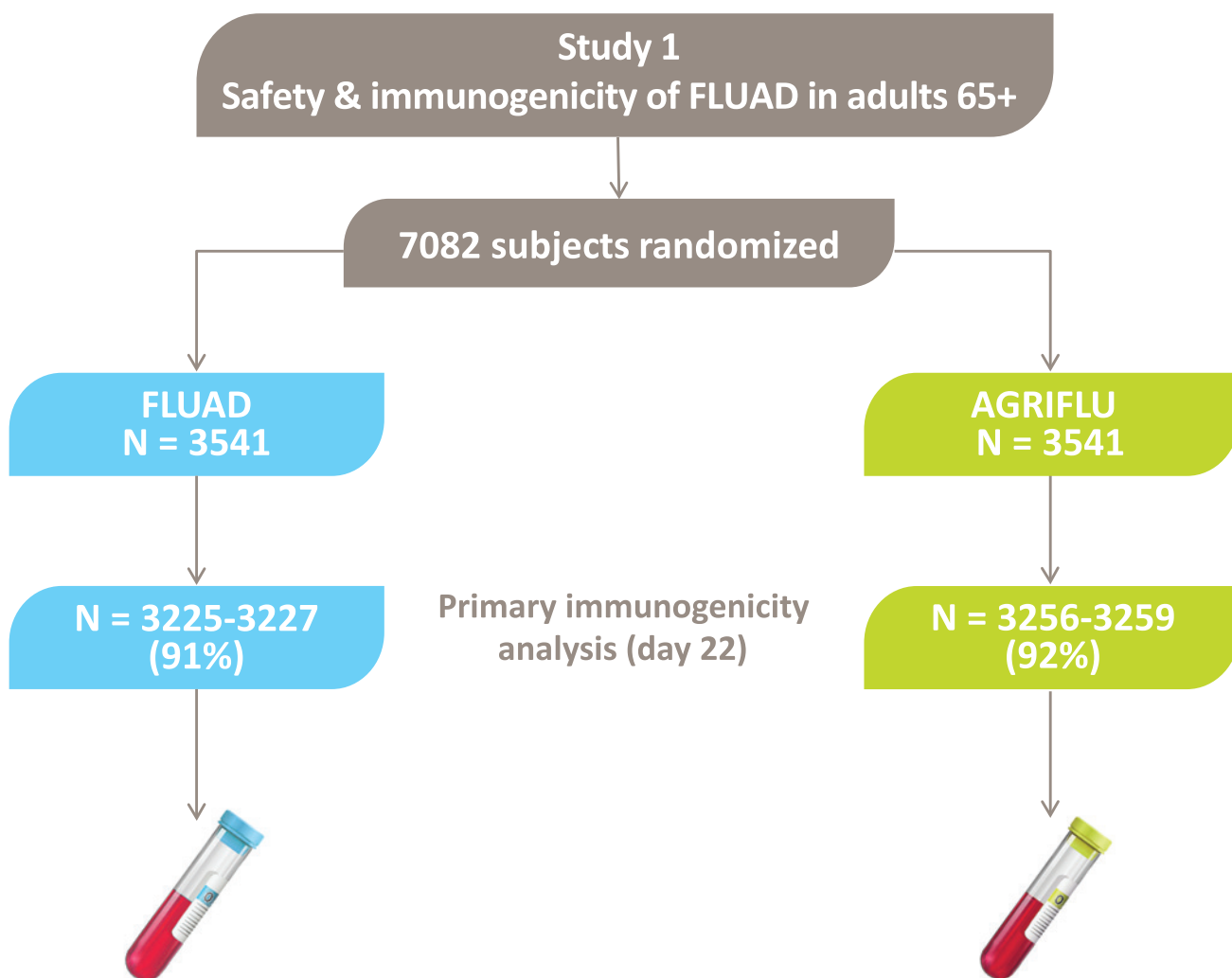
Do not administer FLUAD to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine, including egg protein, or to a previous influenza vaccine.<sup>1</sup>

### FLUAD summary

	FLUAD is an inactivated influenza virus vaccine specifically targeting persons aged 65 years and older. <sup>1</sup>
	Noninferiority of FLUAD in relation to AGRIFLU was established for all 3 vaccine strains on the basis of both seroconversion rates and GMTs. <sup>1</sup>
	In clinical trials, the safety profile of FLUAD was generally similar to that of conventional nonadjuvanted comparators. While higher rates of solicited adverse reactions were noted, they were typically mild to moderate in severity. <sup>1,12</sup>
	FLUAD is a sterile suspension for intramuscular injection supplied in 0.5-mL single-dose prefilled syringes. <sup>1</sup>
	FLUAD is approved in more than 30 countries, and to date more than 81 million FLUAD doses have been distributed worldwide. <sup>13</sup>

## Clinical immunogenicity

Study 1 (NCT01162122) was a multicenter, observer-blind, randomized controlled study that evaluated the safety and immunogenicity of FLUAD in comparison to AGRIFLU. A total of 7082 subjects aged 65 years and older were randomized and vaccinated with FLUAD (N = 3541) or AGRIFLU (N = 3541). The primary immunogenicity analysis was performed on all vaccinated subjects who had a blood sample collected at day 22 (N = 3225-3227 [91%] and 3256-3259 [92%] in the FLUAD and AGRIFLU groups, respectively). A determination of noninferiority was made on the basis of predefined thresholds for seroconversion rate differences and GMT ratios (**Figure 4**).<sup>1</sup>



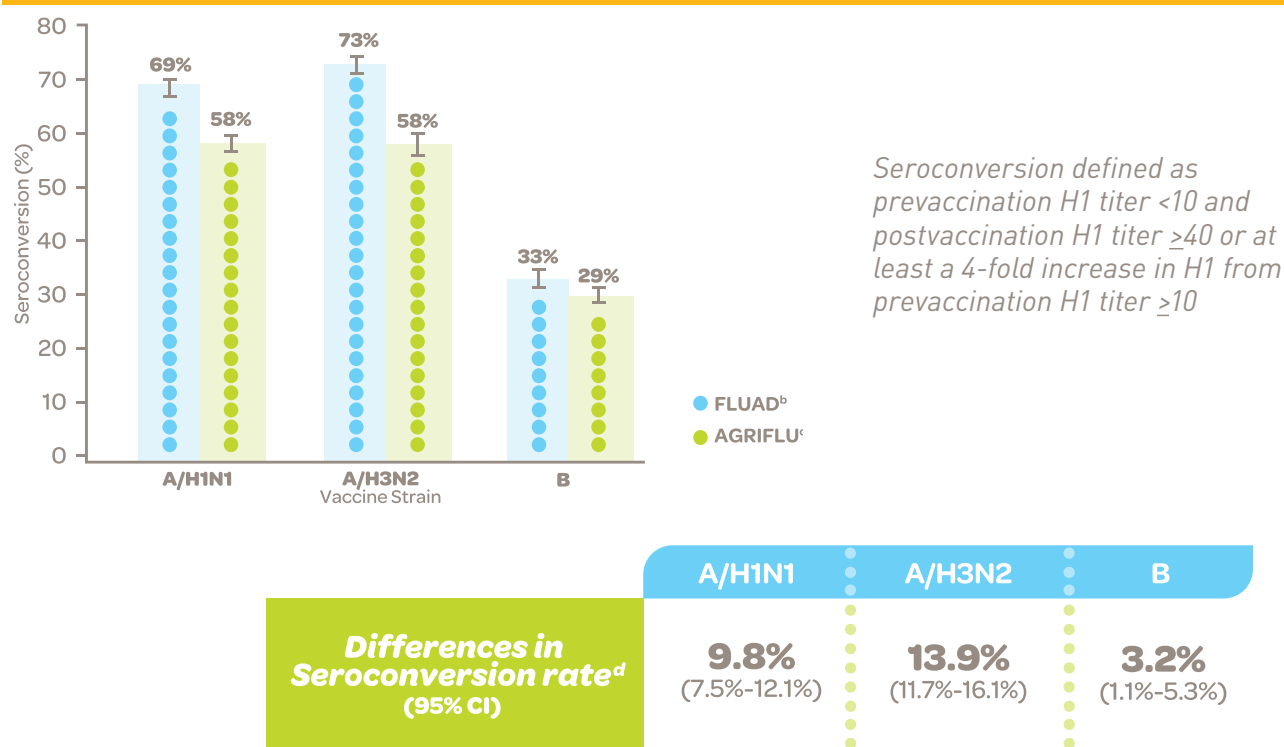
**Figure 4.** FLUAD clinical study design.<sup>1</sup>



FLUAD was evaluated in a pivotal, randomized controlled, observer-blinded clinical trial that included 7082 subjects and has been shown to be immunogenic in adults aged 65 years or older.<sup>1</sup>

As shown in **Figures 5 and 6**, noninferiority of FLUAD in relation to AGRIFLU was established for all 3 vaccine strains on the basis of both seroconversion rates and GMTs.<sup>1</sup>

### Noninferiority Established Based on Seroconversion Rates at Day 22<sup>a</sup>

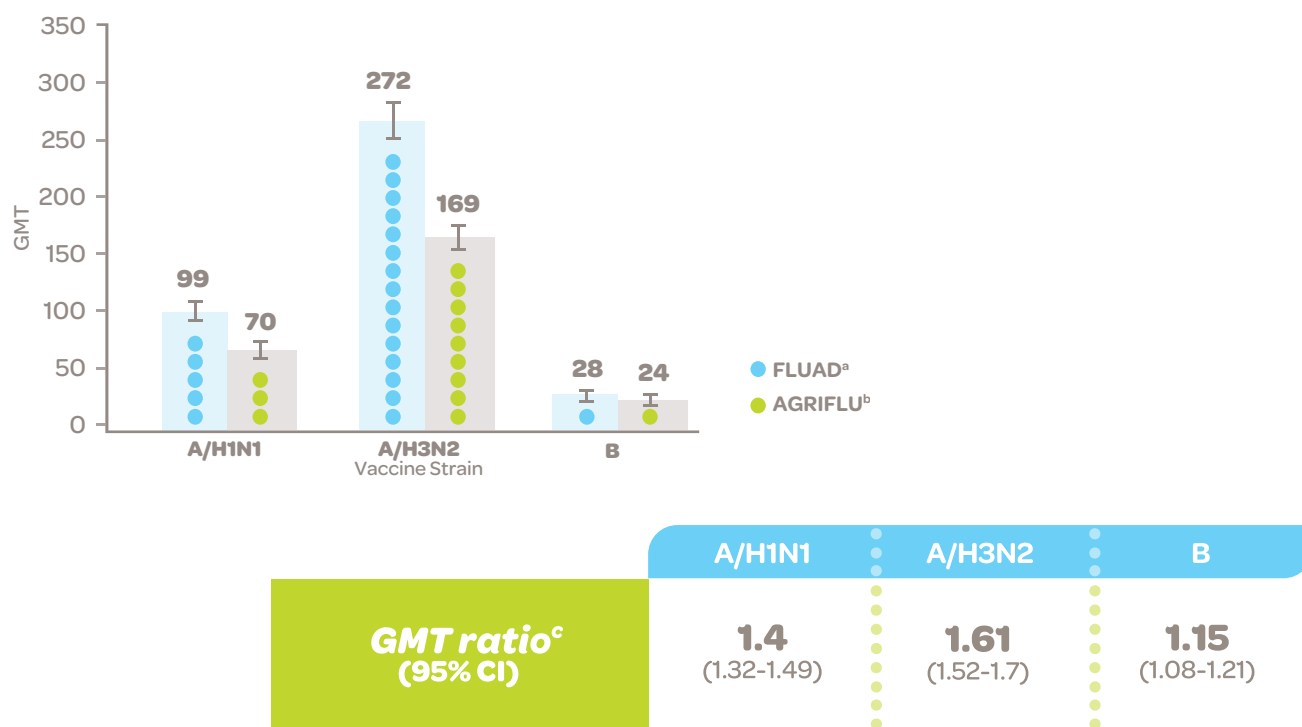


CI, confidence interval.

<sup>a</sup> Results obtained following vaccination with influenza vaccine formulated for the 2010-2011 season. <sup>b</sup> N = 3225-3227, the number of vaccinated participants with available data for the immunologic endpoint listed. <sup>c</sup> N = 3256-3259, the number of vaccinated participants with available data for the immunologic endpoint listed. <sup>d</sup> FLUAD met noninferiority criteria based on seroconversion rate differences if the lower limit of the 95% CI [FLUAD - AGRIFLU] for each strain was  $> -10\%$ .

**Figure 5.** Percentage (95% CI) of subjects 65 years of age and older with seroconversion against 3 influenza strains and differences in seroconversion rates.<sup>1</sup>

## Noninferiority Established Based on GMTs and GMT Ratios at Day 22



GMT, geometric mean antibody titer.

<sup>a</sup> N = 3225-3227; this is the number of vaccinated participants with available data for the immunologic endpoint listed. <sup>b</sup> N = 3256-3259; this is the number of vaccinated participants with available data for the immunologic endpoint listed. <sup>c</sup> FLUAD met noninferiority criteria based on GMT ratios if the lower limit of the 95% CI [FLUAD: AGRIFLU] for each strain was >0.67.

**Figure 6.** GMTs against each vaccine strain (95% CI) and GMT ratios.<sup>1</sup>

## Safety and tolerability of FLUAD

### Solicited adverse events in the pivotal trial

Solicited adverse reactions were assessed in a multicenter, observer-blinded, randomized controlled study (Study 1) in which adults aged 65 years or older received FLUAD (N = 3545) or AGRIFLU (N = 3537). The enrolled subject population in the study was aged 65 to 97 years (mean 72 years) and 64% were women (**Table 1**).<sup>1</sup> Solicited local and systemic adverse reactions were collected from subjects in the study who completed a symptom diary card for 7 days following vaccination.<sup>1</sup>

**Table 1.** Safety population in Study 1.<sup>1</sup>

	Study 1
<b>Mean age, y (range)</b>	72 (65-97)
<b>Female, %</b>	64
<b>Ethnicity, %</b>	
Asian	53
Caucasian	28
Hispanic	18
Black	1
Native American/Alaskan	<1
Pacific Islander/Hawaiian	<1
Other	<1

In the pivotal phase 3 study, the most common ( $\geq 10\%$ ) solicited local adverse reactions in elderly adults ( $\geq 65$  years) were pain (25%) and tenderness (21%) (**Table 2**).<sup>1</sup>

**Table 2.** Percentage of subjects  $\geq 65$  years of age with solicited local adverse reactions in days 1-7 after administration of FLUAD or AGRIFLU.<sup>1</sup>

		FLUAD N <sup>b</sup> = 3418-3496 %	AGRIFLU <sup>a</sup> N <sup>b</sup> = 3420-3488 %
<b>Injection site pain</b>	Any	25.0	12.2
	Moderate <sup>c</sup>	3.9	1.9
	Severe <sup>d</sup>	0.3	0.2
<b>Tenderness</b>	Any	21.1	11.2
	Moderate	3.0	1.0
	Severe	0.1	0.2
<b>Erythema</b>	Any	1.2	0.5
	25 to $\leq 50$ mm	1.1	0.5
	51 to $\leq 100$ mm	0.2	<0.1
	>100 mm	0.0	0.0
<b>Induration</b>	Any	1.3	0.5
	25 to $\leq 50$ mm	1.0	0.5
	51 to $\leq 100$ mm	0.3	0.0
	>100 mm	0.0	0.0
<b>Swelling</b>	Any	1.2	0.4
	25 to $\leq 50$ mm	1.0	0.4
	51 to $\leq 100$ mm	0.2	<0.1
	>100 mm	<0.1	0.0

<sup>a</sup> AGRIFLU (influenza vaccine) is a US-licensed nonadjuvanted influenza vaccine. <sup>b</sup> N = number of subjects with safety data. <sup>c</sup> Moderate: pain, tenderness, myalgia, fatigue, headache, arthralgia, chills, nausea, vomiting defined as "some limitation in normal daily activity," diarrhea defined as "4 to 5 stools a day." <sup>d</sup> Severe: pain, tenderness, myalgia, fatigue, headache, arthralgia, chills, nausea, vomiting defined as "unable to perform normal daily activity," diarrhea defined as "6 or more watery stools a day."



In the pivotal phase 3 study, the most common solicited systemic adverse reactions observed were myalgia (15%), headache (13%), and fatigue (13%) (**Table 3**).<sup>1</sup>

**Table 3.** Percentage of subjects aged ≥65 years with solicited systemic adverse reactions in days 1-7 after administration of FLUAD or AGRIFLU.<sup>1</sup>

		FLUAD N <sup>b</sup> = 3418-3496 %	AGRIFLU <sup>a</sup> N <sup>b</sup> = 3420-3488 %
<b>Myalgia</b>	Any	14.7	9.7
	Moderate <sup>c</sup>	2.6	1.8
	Severe <sup>d</sup>	0.3	0.7
<b>Fatigue</b>	Any	13.3	10.4
	Moderate	3.1	2.4
	Severe	0.4	0.6
	PLT <sup>e</sup>	0.0	<0.1
<b>Headache</b>	Any	13.2	11.2
	Moderate	3.0	2.6
	Severe	0.4	0.6
	PLT	0.0	<0.1
<b>Arthralgia</b>	Any	8.5	7.8
	Moderate	1.6	1.6
	Severe	0.2	0.6
<b>Chills</b>	Any	6.7	4.7
	Moderate	1.5	1.2
	Severe	0.3	0.3
	PLT	<0.1	0.0
<b>Diarrhea</b>	Any	4.8	4.5
	Moderate	1.3	0.9
	Severe	0.3	0.2
	PLT	<0.1	<0.1
<b>Fever</b>	Any	3.6	3.4
	≥38.0°C to ≤38.4°C	1.8	1.7
	≥38.5°C to ≤38.9°C	1.3	1.3
	39.0°C to ≤40.0°C	0.4	0.4
	≥40.0°C	0.1	0.0
<b>Nausea</b>	Any	2.9	2.8
	Moderate	0.4	0.6
	Severe	0.1	0.1
	PLT	<0.1	0.0
<b>Vomiting</b>	Any	1.4	1.7
	Moderate	0.4	0.5
	Severe	<0.1	0.1
	PLT	<0.1	0.0

<sup>a</sup> AGRIFLU (influenza vaccine) is a US-licensed nonadjuvanted influenza vaccine. <sup>b</sup> N = number of subjects with safety data. <sup>c</sup> Moderate: pain, tenderness, myalgia, fatigue, headache, arthralgia, chills, nausea, vomiting defined as "some limitation in normal daily activity," diarrhea defined as "4 to 5 stools a day." <sup>d</sup> Severe: pain, tenderness, myalgia, fatigue, headache, arthralgia, chills, nausea, vomiting defined as "unable to perform normal daily activity," diarrhea defined as "6 or more watery stools a day." <sup>e</sup> Potentially life-threatening (PLT) reaction defined as requiring emergency room visit or hospitalization.

While higher rates of solicited adverse reactions were noted, they were typically mild to moderate in intensity.<sup>1,12</sup>

# FLUAD: SAFETY DATA FROM 15 RANDOMIZED CONTROLLED STUDIES IN MORE THAN 10,000 ADULTS 65+

## Unsolicited adverse events and adverse events of special interest

The clinical safety of FLUAD was assessed in 15 randomized controlled studies. The total safety population in these trials included 10,952 adults 65 years and older, 5754 who received FLUAD and 5198 who received other US-licensed influenza vaccines. The percentage of subjects with an unsolicited adverse event (AE) within 30 days following vaccination was similar between vaccine groups.<sup>1</sup> In addition, rates of new-onset neuroinflammatory and immune-mediated diseases were assessed in a post hoc analysis of the 15 randomized controlled studies over 1 year. The percentage of subjects with an adverse event of special interest (AESI) at any time after vaccination was also similar between vaccine groups. There were no notable imbalances for specific AESIs (Table 4).<sup>1</sup>

Table 4. Unsolicited AEs and AESIs in 15 randomized controlled trials.<sup>1</sup>

	FLUAD N = 5754 %	Comparator <sup>a</sup> N = 5198 %
Unsolicited AE	16.9	18.0
AESI	0.9	0.9

<sup>a</sup> Other US-licensed influenza vaccines.

## Serious adverse events and deaths

Subjects in Study 1 were followed for 1 year following vaccination. The percentages of subjects with an SAE were similar between vaccine groups. Four SAEs (1 FLUAD and 3 AGRIFLU) were considered to be related to study vaccination over 1 year of observation; 2 of these occurred (1 FLUAD, 1 AGRIFLU) within 21 days of vaccination. There were 98 deaths (n = 52 FLUAD, n = 46 AGRIFLU) that occurred within 1 year of vaccination; however, none occurred within 21 days of vaccination (Table 5).<sup>1</sup>

Table 5. SAEs and deaths in Study 1.<sup>1</sup>

	FLUAD N = 3545	AGRIFLU N = 3537
SAE, %	7	7
Deaths, n	52	46

The number of SAEs and deaths were also monitored in 14 additional randomized controlled studies. The percentages of SAEs and deaths within 30 days and within 6 months were similar between vaccine groups (Table 6).<sup>1</sup>

Table 6. SAEs and deaths in 14 randomized controlled studies.<sup>1</sup>

	FLUAD N = 2209		Comparator <sup>a</sup> N = 1661
Percentage of subjects with SAEs			
Within 30 days	1.1		1.8
Within 6 months	4.3		5.9
Percentage of deaths			
Within 30 days	0.3		0.6
Within 6 months	1.0		1.5

<sup>a</sup> The comparator for SAEs was AGRIFLU; the comparator for deaths was other US-licensed vaccines.

### Safety of annual revaccination

In 5 of the randomized controlled trials, subjects were followed for SAEs and deaths for 6 months following revaccination. The percentages of subjects with an SAE reported after the second annual revaccination was similar between groups. None of the 23 reported deaths were considered to be related to study vaccination (Table 7).<sup>1</sup>

Table 7. SAEs and deaths reported after second annual vaccination with FLUAD or comparator influenza vaccines.<sup>1</sup>

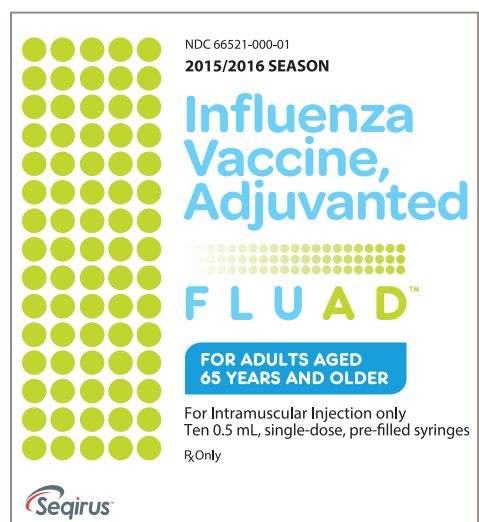
	FLUAD N = 492		Comparator <sup>a</sup> N = 330
SAE, %	6.1		5.5
Deaths, n	17		6

<sup>a</sup> US-licensed and non-US-licensed influenza vaccines.

## Dosage and administration<sup>1</sup>

- FLUAD is a sterile suspension supplied in 0.5-mL single-dose prefilled syringes.
- Gently shake each syringe. FLUAD has a milky white appearance. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either condition exists, FLUAD should not be administered.
- The vaccine should be administered by intramuscular injection, preferably in the region of the deltoid muscle of the upper arm. Do not inject the vaccine in the gluteal region or areas where there may be a major nerve trunk.

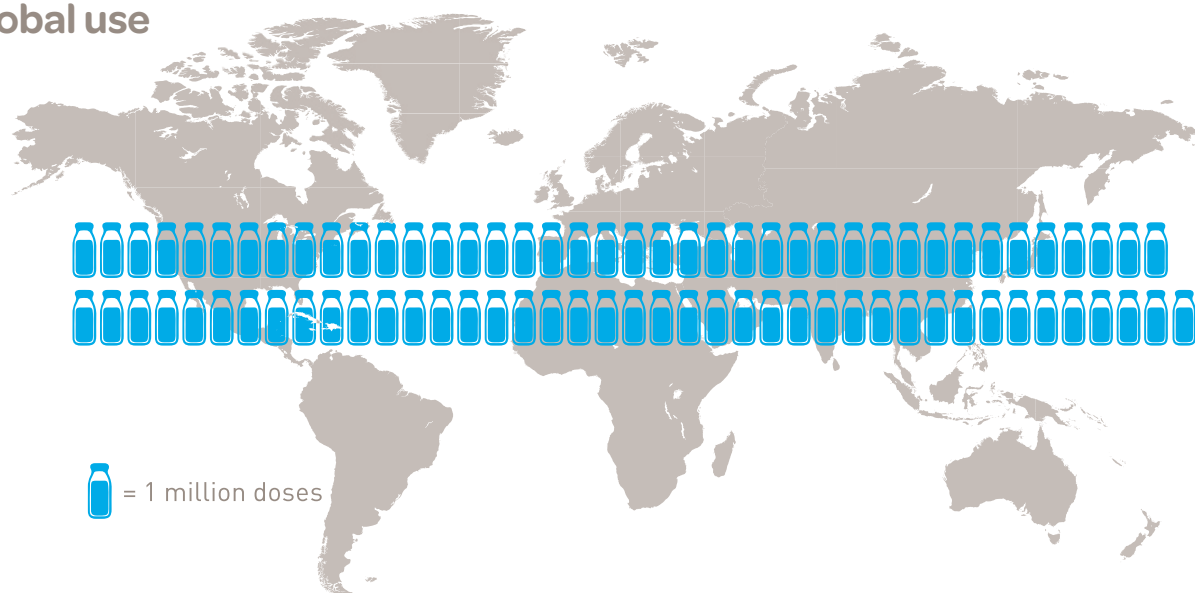
## How supplied/storage and handling<sup>1</sup>



- FLUAD is supplied as a 0.5 mL prefilled needleless syringe in the following format:
  - Package of 10 prefilled syringes per carton (NDC number: 66521-000-01)
- Do not use after expiration date.
- Store in a refrigerator (2°C-8°C [36°F-46°F]).
- Do not freeze. Discard if the vaccine has been frozen.
- Protect from light.

CPT code 90653

## Global use



FLUAD is approved in more than 30 countries, and to date more than 81 million FLUAD doses have been distributed worldwide.<sup>13</sup>

## Important Safety Information

### INDICATIONS AND USAGE

FLUAD is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD is approved for use in persons 65 years of age and older.<sup>1</sup>

### CONTRAINDICATIONS

Severe allergic reaction to any component of the vaccine, including egg protein, or after a previous dose of any influenza vaccine.<sup>1</sup>

### WARNINGS AND PRECAUTIONS<sup>1</sup>

- If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give FLUAD should be based on careful consideration of the potential benefits and risks.
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

### ADVERSE REACTIONS<sup>1</sup>

- The most common ( $\geq 10\%$ ) local (injection-site) adverse reactions observed in clinical studies were injection site pain (25%) and tenderness (21%).
- The most common ( $\geq 10\%$ ) systemic adverse reactions observed in clinical studies were myalgia (15%), headache (13%) and fatigue (13%).

**Please see accompanying US full Prescribing Information for FLUAD.**

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November 2015

GMCC-637 2015-01-13

