OBE/DE REVIEW MEMO

DATE: 27-FEB-2009

STN: 125297\0

SPONSOR: Novartis Vaccines and Diagnostics, Inc.

PRODUCT: Agrippal® (Influenza Vaccine Surface Antigen Inactivated, IVV)

Active ingredients:
Surface antigens (15 µg of haemagglutinin) of each of three influenza strains including H1N1, H3N2, and B, based upon seasonal requirements (U.S. recommendations will be according to USPHS requirements)

Excipients:
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Dose:
0.5 ml for adults and children 3 years of age and older
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A second dose is recommended at least 4 weeks after the first dose in children

Route: Intramuscular (IM) or deep subcutaneous (SQ)

TO: Anissa M. Cheung, DVP, BLA Chair (HFM-445)

FROM: Patricia Rohan, MD (HFM-222)

THROUGH: Andrea Sutherland, MD, Acting Chief, Vaccine Safety Branch (HFM-222)

Robert Wise, MD, MPH, Acting Director, Div. of Epidemiology (HFM-220)

CC: Chronological File (HFM-220)

BLA RECEIVED: 11-JUL-2008

FIRST ACTION DUE: 11-MAY-2009

1. BACKGROUND:

1.1. GENERAL

Influenza

Influenza is a highly infectious, acute viral infection spread through person-to-person contact, specifically, through respiratory droplets, e.g., cough or sneeze. Each year, influenza infects 5-20% of the population and resulting in 17,000-51,000 deaths and 55,000-431,000 hospitalizations in the US, and 250,000-500,000 deaths worldwide each year. The highest rates of illness are seen in children 5-14 years of age and more severe and fatal outcomes are seen in children < years of age, older adults ≥ 65 years of age and those with chronic medical conditions. In the U.S., over 90% of deaths occur in those ≥ 65 years of age.

Influenza-related morbidity and mortality are difficult to estimate as they are due not only to the viral infection itself, but also indirectly to the disease's impact on individuals with cardiopulmonary and other underlying disease and to secondary post-viral infections, most notably pneumonia.

Influenza virus circulate throughout the world in a seasonal pattern, i.e., the winter months in the Northern Hemisphere, and disease is notably affected by antigenic drift (including point mutations, substitutions, deletions and insertions in the viral genome) and antigenic shifts (recombinant and reassortment based changes due to co-circulation of multiple influenza A strains in humans or animals and/or transmission from an animal reservoir to humans, e.g., avian influenza A - H5N1 and H9N2). These genetic changes affect two surface glycoproteins of the virus, hemagglutinin (HA) and neuraminidase (NA). Individuals with immunity to a particular strain may be susceptible to infection with the resulting new viral type or subtype, and influenza vaccines are necessarily re-formulated annually to best match the anticipated circulating viruses based upon the recommendations of The World Health Organization (WHO).

Two approaches are available to deal with influenza infections - treatment and prevention. Antiviral drugs are licensed to both prevent and treat influenza, but are limited by development of drug resistant virus, adverse drug reactions, by actual level of effectiveness and by the need for dose adjustment in those with renal insufficiency, notably in the elderly. Vaccination is the principal method of influenza disease control and is currently recommended by the U.S. Center for Disease Control's (CDC's).Advisory Committee on Immunization Practices (ACIP) annually for children 6 months -18 years of age, pregnant women, those 50 years of age and older and those with certain chronic medical conditions and those in close contact with persons at higher risk of influenza-related complications. There are six currently licensed trivalent influenza vaccines in the U.S. – Afluria (CSL), Fluarix (GSK), FluLaval (GSK, formerly ID Biomedical), Fluvirin (Novartis), Fluzone (sanofi pasteur) and FluMist (MedImmune). All of these products are manufactured in hen eggs.

Neutralizing antibodies against hemagglutinin (HA) are considered protective against infection, and vaccine studies employ HA antibody titers as a surrogate, albeit an inexact one, to predict efficacy as the relationship between antibody levels or titers and protection appears to vary among subpopulations, most notably the elderly.

1.2. PRODUCT

Agrippal® (IVV) is a trivalent, inactivated influenza vaccine (TIV) initially licensed in Italy on 11-OCT-1986. It is currently licensed in more than 50 countries worldwide including 15 EU

countries by Mutual Recognition Procedure (MRP) and countries in Africa, Asia, Central and South America and Asia. More than --b(4)---- doses are reported to have been sold since initial licensure, including ---b(4)------ doses since 2003, when IVV formulation was changed to thimerosal-free. A total of 545 AE reports have been received by the company (--b(4)----------doses distributed) since 2003.

The sponsor reports no label changes have been made or are under consideration based upon safety concerns. There are no events from clinical studies or post-marketing surveillance which required or would require risk mitigation activities.

1.3. Current Label Safety Information

IVV is not currently licensed in the U.S.

Common adverse events from clinical trials (>1/100, <1/10)
Solicited reactions (Usually disappear within 1-2 days without treatment)

- Local reactions: redness, swelling, pain, ecchymosis, induration.
- Systemic reactions: fever, malaise, shivering, fatigue, headache, sweating, myalgia, arthralgia.

Adverse events reported from post-marketing surveillance:

- Generalised skin reactions including pruritus, urticaria or non-specific rash.
- Transient thrombocytopenia, transient lymphadenopathy
- Allergic reactions, in rare cases leading to shock, angioedema
- Vasculitis associated in very rare cases with transient renal involvement
- Neuralgia, paraesthesia, febrile convulsions, neurological disorders, such as encephalomyelitis, neuritis and Guillain-Barré Syndrome

The vaccine may contain residues of the following substances, e.g. eggs, chicken proteins, kanamycin and neomycin sulphate, formaldehyde cetyltrimethylammonium bromide (CTAB) and polysorbate 80.

2. Safety Specification

2.1 Non-clinical.

These studies are reviewed elsewhere and are summarized for this review.

- non-GLP studies have demonstrated immunogenicity in mice, rabbits and ferrets
- Typical pharmacology studies were not conducted on the product
- GLP repeat-dose toxicity studies in rabbits using 45ug x 2 doses showed injection site reactions but no treatment-related abnormalities (clinical and selected histology)

- Two GLP repeat dose, reproductive toxicity studies in female rabbits using 0.5 mL x 5 (presumably 45 ug), approximately 2 weeks apart, three doses prior to mating and two during gestation. No maternal or fetal toxicity, teratogenicity or developmental abnormalities were observed.

2.2 Clinical Trials

2.2.1 Pivotal Studies

The following table summarizes the two clinical safety and immunogenicity studies intended to support the licensure of Agrippal.

Table 1: Overview of Pivotal Studies in Support of this BLA

Study	V71P5			V71P6		
Location	Argentina (2 sites)			Dominican Republic (single site)		
Study Period	11-APR-2007 through 20-DEC-2007			12-NOV-2007 through 21-DEC-2007		
Design	Phase 3, observer-blind, randomized, controlled, study of safety, tolerability and immunogenicity			Phase 3 observer-blinded, randomized, controlled, single-center study of safety, tolerability, immunogenicity, and lot-to-lot consistency		
Vaccine	IVV* or Fluvirin, 0.5 mL IM Adults/adolescents: single dose Children: 2 doses, 4 wks. apart			IVV* or Fluvirin, 0.5 mL IM Single dose		
Population	Healthy subjects			Healthy Subjects		
	Adults	18-64 yrs.	N = 692	Adults	18-49 yrs.	N = 1507
	Adolescents	9-17 yrs.	N = 600			
	Children	3-8 yrs.	N = 601			
Demographics	64% female, 36% male 80% Caucasian, 20% Hispanic, <1% Asian			72% female, 28% male 98% Hispanic, 2% Black, <1% Caucasian, <1% Other		
Follow-up	6 months			6 months		

*Thimerosal free

From BLA 125297, Appendix 1.16, page 4, Table 1

Study: V71P6

Title: A Phase III, Randomized, Controlled, Observer-Blind, Single-Center Study to Evaluate the Consistency of Three Consecutive Lots of a Trivalent Subunit Influenza Vaccine Produced in Embryonated Hen Eggs in Healthy Subjects Aged 18 to 49 Years (Dominican Republic)

Changes to Protocol related to safety evaluations

Amendment Number 1 (11-SEP-2007)

Increased enrollment of subjects 18-49 years of age from 700 subjects to 1500 subjects, including 1284 subjects randomized to receive IVV (428 subjects for each of three lots) and 216 subjects randomized to receive Fluvirin using CBER criteria for influenza vaccine studies.

Amendment Number 3 (16-APR-2008)

Final immunogenicity and safety analysis from data after visit 2 (Day 22), as requested by FDA/CBER

Enrolled: 1507 subjects enrolled
Randomization: 2:2:2:1 to receive a single dose of one of three lots IVV or Fluvirin
Study Period: 12-NOV-2007 through 21-DEC-2007
Population: Adult subjects 18-49 years of age
Vaccination: Single dose 0.5 mL trivalent influenza vaccine (IVV or Fluvirin)
Strains recommended for 2007-2008 season in the Northern Hemisphere

Follow-up: 26 weeks post-vaccination

Table 1: Demographic and Other Baseline Characteristics by Vaccine Group – V71P6

		Lot A N=430	Lot B N=431	Lot C N=429	pooled IVV N=1290	Fluvirin N=217
Age (Years)	Mean ± SD	31.1±8.8	31.2±8.6	31.3±8.9	31.2±8.8	31.3±8.7
Sex	Male	121 (28%)	125 (29%)	138 (32%)	384 (30%)	63 (29%)
	Female	309 (72%)	306 (71%)	291 (68%)	906 (70%)	154 (71%)
Ethnic Origin	Arabic	1 (<1%)	0	0	1 (<1%)	0
	Black	7 (2%)	11 (3%)	9 (2%)	27 (2%)	3 (1%)
	Caucasian	1 (<1%)	2 (<1%)	1 (<1%)	4 (<1%)	0
	Hispanic	421 (98%)	418 (97%)	418 (97%)	1257 (97%)	214 (99%)
	Native American/ Alaskan	0	0	1 (<1%)	1 (<1%)	0
Prev. Flu Vaccine:	No	427 (99%)	431 (100%)	429 (100%)	1287 (99.9%)	216 (99.9%)
	Unknown	3 (<1%)	0	0	3 (<1%)	1 (<1%)
STN 125287 Clinical Study Report V71P6, Table 11.2-1						

Table 2: Subject Disposition - V71P6

	IVV				Fluvirin
	Total	Lot A	Lot B	Lot C	
Enrolled	1290	430	431	429	217
Vaccinated	1277	423	426	428	216
Included in Safety Analysis	1209	403	404	402	202
STN 125287 V71P6 Clinical Study Report, Table 11.1-1					

Safety Results

1. Solicited Local Reactions

Similar percentages of subjects in each of the 3 IVV lot groups reported any solicited local reactions (range, 24% to 28%). The proportion of subjects reporting any solicited local reaction was similar for the pooled IVV lot group and Fluvirin group. The most commonly reported solicited local reaction, pain, was reported by 21% to 24% of subjects in the three IVV lot groups. Only one solicited event, pain, was rated as severe and occurred in ≤ 1% of recipients in each of the three IVV Lot groups. The proportion of subjects reporting any solicited local reaction and proportion reporting each type of solicited event were similar for the pooled IVV lot groups and the Fluvirin group (26% and 27%, respectively). The most commonly reported solicited local reaction was pain which was reported by 22% of both of the pooled IVV group and the Fluvirin group. No more than 1% of recipients of the pooled IVV or Fluvirin grip[s reported severe pain and no subjects reported other severe solicited local reactions. Most solicited local reactions were transient, occurring during the first 4 days postvaccination ≤ 2% pooled IVV group and 3% of the Fluvirin recipients) were reported during days 5 to 7.

2. Solicited Systemic Reactions

The percentages of subjects reporting any solicited systemic reactions were the same among each of the 3 IVV lot groups (37%). The most commonly reported solicited systemic reaction was headache which was reported by between 23% to 25% in each of the three IVV lot groups. Less than 1% of these reports were graded as severe in the three IVV lot groups, except for headache (2% of Lot B group).

Fever (defined as axillary temperature ≥ 38°C) was reported by 3% to 6% of subjects in the IVV lot groups. Only two subjects, both recipients of IVV Lot C reported fevers of 40°C – one subject with onset

on study day 1 and continued for 4 days, and one subject reporting an influenza-like illness with onset on study day 5 and continued for 14 days.

A similar proportion of subjects reported staying at home due to a reaction in the three IVV lot groups (range, 6% to 8%), the pooled IVV group (7%) and the Fluvirin vaccine (9%). No more than 10% of subjects used analgesics/antipyretic after injection in any group.

The proportion of subjects reporting any solicited systemic reaction was similar between the three IVV lot groups, the pooled IVV lots and the Fluvirin groups (range, 37-38%) The most commonly reported solicited systemic reaction was headache which was reported by 24% of the pooled IVV group and Fluvirin group. Reactions of severe intensity were reported by no more than 1% of the pooled IVV and Fluvirin groups, except for headache (1% and 2%, respectively). Fever (defined as axillary temperature ≥ 38°C) was reported by 4% of subjects in the pooled IVV group and 3% of Fluvirin group. Only two subjects, both recipients of the pooled IVV group reported fevers of 40°C.

Most solicited systemic reactions were resolved by day 7.

3. Unsolicited Adverse Events
Overall during the first 21 days, unsolicited AEs were similarly experienced by subjects from the three lot groups (range, 14% to 17%). The System Organ Classes (SOCs) most affected were “General Disorders & Administration Site Conditions”, “Nervous System Disorders”, and “Respiratory, Thoracic & Mediastinal Disorders” for the three IVV lots. The most commonly reported SOC affected was “General Disorders and Administration Site Conditions” (2% [10/403] Lot A, 4% [18/404] Lot B and Lot C).

During the first 21 days, the most frequently experienced unsolicited AEs were influenza-like illness, headache, and pharyngolaryngeal pain, for the three IVV lots. Overall during the first 21 days, unsolicited AEs were experienced by the same percentage of subjects from the pooled IVV vaccine group and the Fluvirin vaccine group (16%). The System Organ Classes (SOCs) most affected were “General Disorders & Administration Site Conditions”, “Nervous System Disorders”, and “Respiratory, Thoracic & Mediastinal Disorders” for the pooled IVV vaccine group and Fluvirin vaccine group. The percentages reporting unsolicited AEs by SOCs were similar in the pooled IVV and Fluvirin groups. During the first 21 days, the most frequently experienced unsolicited AEs were influenza-like illness, headache, and pharyngolaryngeal pain, respectively, for the two vaccine groups.

4. Serious Adverse Events
Fourteen SAEs were reported by 10 subjects in the pooled IVV group (4 Lot A, 3 Lot B, 3 Lot C) and 2 subjects in the Fluvirin group. (Table 3)

5. Other Significant Adverse Events
Ten pregnancies reported after vaccination during this study, all 10 in the IVV vaccine group (4, 2, and 4 recipients in Lot A, Lot B, and Lot C, respectively). To date, pregnancy outcomes include 2 Lot A recipients - spontaneous abortion and induced abortion, Lot B recipient - induced abortion and spontaneous abortion (reason unknown as this is the second event during the study for this subject), and Lot C recipient - miscarriage. A study addendum will be submitted after follow-up of all other pregnancies.

6. Deaths
No deaths were reported during the study.

7. Withdrawals Due to AEs
There were no discontinuations from the study due to AEs.

Table 3: Serious Adverse Events - Study V71P6

Subj. No.	Vaccine Group	PT	Onset Study Day	Duration (Days)	Outcome	Hospitalized
110355	Lot A	Abortion Induced	31	<1	Recovered	No

110475	Lot A	Abortion Induced	23	1	Recovered	No
110475[b]	Lot B	Spontaneous Abortion	[b]	[b]	[b]	[b]
100133	Lot C	Headache	1	[4]	Recovered	Yes
100133	Lot C	Pyrexia	1	4	Recovered	Yes
100193	Fluvirin	Cholecystitis	22	1	Recovered	Yes
100629	Lot B	MVA, Spontaneous Abortion	36	1	Recovered	Yes
100206	Lot A	Coccyx fracture, MVA	75	5	Alive, sequelae	Yes
100259	Lot A	Spontaneous Abortion	58	1	Recovered	Yes
110140	Lot B	Uterine Myoma	149	3	Recovered	Yes
110212	Fluvirin	Fibroadenoma	[b]	[b]	Recovered	Yes
110250	Lot C	Cholelithiasis	[b]	[b]	Recovered	Yes
100336	Lot A	Goiter	[b]	[b]	Recovered	Yes
110122	Lot B	Hysterectomy	27	1	Recovered	Yes

BLA 125279 Clinical Study Report V71P6, Table 12.3.1.2-1
a - a SAEs reported the between database lock and the cut-off date as of 31 May 2008
b - data not yet available as source from ongoing follow-up data

8. Pregnancies
10 individuals reported pregnancy
Lot A 4 (1 miscarriage, 1 abortion)
Lot B 2 (1 miscarriage, 1 abortion – both in same subject)
Lot C 4 (1 miscarriage), Fluvirin 0
At time of this report – 6 pregnancy outcomes are unknown

V71P5
A Phase III Observer-Blind, Randomized, Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Immunogenicity of Two Trivalent Subunit Inactivated Influenza Vaccines (Agrippal™ and Fluvirin™) in Healthy Children Aged 3 to 8 years, in Healthy Children/Adolescents Aged 9 to 17 Years And in Healthy Adults Aged 18 to 64 Years (Cordoba, Argentina and Buenos Aires, Argentina)

Changes to the protocol
1. Change age cohorts from 3-8 years, 18-64 years and ≥65 years; to 3-8 years, 9-17 years and 18-64 years
2. Change immunogenicity population to include only individuals 18-64 years of age.

Study Plan
Enrolled: 1800 subjects
Randomization: 2:1 to receive a single dose of IVV or Fluvirin
Study Period: 11-APR-2007 through 20-DEC-2007
Population: 3-8 years of age, 9-17 years of age and 18-64 years of age
Vaccination:

Adults & adolescents:	Single dose 0.5 mL trivalent influenza vaccine (IVV or Fluvirin)
Children 3-8 years of age:	Two dose 0.5 mL trivalent influenza vaccine (IVV or Fluvirin) 4 weeks apart

Strains recommended for 2007-2008 season in the Northern Hemisphere

Safety Evaluations
Solicited AEs for 7 days post-vaccination
All AEs for 21 days post-vaccination

SAEs, AEs that led to withdrawal from the study, and medically significant AEs (e.g., new onset chronic illness) from 21 days after last vaccination to end of study

Clinic Visits
Day 0: vaccination
Day 22 clinic visit (9-17 yr. olds, 18-64 yr. olds): blood draw
Days 29 clinic visit (3-8 yr. olds): vaccination, blood draw
Day 50 clinic visit (3-8 yr. olds): blood draw
Final follow-up by phone: 6 month post-vaccination

Demographics
The majority of subjects in all three age strata were Caucasians: 78% to 80% for the adult age stratum, and, notably 100%, for both the adolescent and children age strata. The adult age stratum also included 20-22% Hispanic. Less than 1% of adult subjects were Asian. No Black subjects were enrolled in any of the age cohorts.

Table 4: Demographic and Other Baseline Characteristics by Vaccine Group – V71P5

		3-8 years		9-17 years		18-64 years	
		Agrippal N = 402	Fluvirin N = 199	Agrippal N = 400	Fluvirin N= 200	Agrippal N=460	Fluvirin N = 232
Age (Years)	Mean ± SD	5.5±1.7	5.4±1.7	12.7±2.6	12.8±2.6	38.8±12.4	37.8±12.6
Sex	Male	230(57%)	101(51%)	178(45%)	91(46%)	167(36%)	102(44%)
	Female	172(43%)	98(49%)	222(56%)	109(55%)	293(64%)	130(56%)
Ethnic Origin	Caucasian	402 (100%)	199 (100%)	400 (100%)	200 (100%)	366(80%)	180(78%)
	Hispanic	0	0	0	0	92 (20%)	52 (22%)
	Asian	0	0	0	0	2 (<1%)	0
	Black	0	0	0	0	0	0
	Other	0	0	0	0	0	0
Prev. Flu Vaccine:	Yes	N/A	N/A	8 (2%)	4 (2%)	101 (22%)	49 (21%)
	No	N/A	N/A	392 (98%)	196 (98%)	342 (74%)	175 (75%)
	Unknown	N/A	N/A	0	0	17 (4%)	8 (3%)

STN 125287 Clinical Study Report V71P5, Table 11.2-1

Table 5: Subject Disposition - V71P5

	3-8 years		9-17 years		18-64 years	
	Agrippal	Fluvirin	Agrippal	Fluvirin	Agrippal	Fluvirin
Enrolled	402	199	400	200	460	232
Vaccinated	402	199	400	200	460	232
Included in Safety Analysis	402	199	400	199	460	233*

*One adult subject was mistakenly enrolled in 9-17 year age group, but included 18-64 age group analyses.
STN 125287 V71P5 Clinical Study Report, Table 11.1-1

Safety results
1. Adult 18 to 64 years of age:
A total of 50% of Agrippal recipients and 55% of Fluvirin recipients reported at least one solicited local or systemic reaction, which by definition onset within 7 days of vaccination. No more than 1% of each solicited local or systemic reactions were classified as severe in either vaccine group. Few continued past the day 7 observation window and all had resolved by the end of the study.

Pain (25% in Agrippal and 30% in Fluvirin groups) was the most common solicited local reaction and headache (23% in Agrippal and 18% in Fluvirin groups) the most common solicited systemic reaction in

both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups (50%: Agrippal and 55%: Fluvirin). Fever (defined as axillary temperature ≥38°C) was reported by a similar percentage of subjects in both vaccine groups (2% Agrippal and 3% Fluvirin). One subject in the Agrippal group reported a temperature ≥ 40°C in conjunction with an influenza-like illness with onset on study day 2 and duration of 5 days.

The percentages of subjects with nonsolicited AEs were balanced between the groups (19% Agrippal vs. 20% Fluvirin).

No death or AE leading to a subject's withdrawal from the study was reported during the study.

Within the adult cohort were eight subjects who reported eight SAEs. (See Table 6, below)

2. Adolescents 9 to 17 years of age:
A total of 42% of Agrippal recipients and 41% of Fluvirin recipients reported at least one solicited local or systemic reaction, which by definition onset within 7 days of vaccination. No more than 1% of each solicited local or systemic reactions were classified as severe in either vaccine group. Most reactions resolved within the 7-day observation window and all had resolved by the end of the study.

Pain (29% in both vaccine groups) was the most common solicited local reaction and headache (11% to 13%) the most common solicited systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups. Fever (defined as axillary temperature ≥38°C) was reported by a similar in both vaccine groups (<1% Agrippal and 2% Fluvirin). No subjects reported body temperature ≥ 40°C.

The percentages of subjects with nonsolicited AEs were similar between the groups (6% Agrippal vs. 10% Fluvirin).

No death or AE leading to a subject's withdrawal from the study was reported during the study.

There were four subjects who reported four SAEs. (See Table 6, below)

3. Children 3 to 8 years of age
A total of 32% of Agrippal recipients and 37% of Fluvirin recipients, after first injection and 22% of Agrippal recipients and 23% of Fluvirin recipients, after second injection, reported at least one solicited local or systemic reaction, which by definition onset within 7 days of vaccination. No more than 1% of each solicited local or systemic reaction classified as severe in either vaccine group. They mostly were transient with few continuing past the day 7 observation window and none continued at the end of the study.

Pain (24% in Agrippal and 30% in the Fluvirin groups) was the most common solicited local reaction and headache (10% to 13%) the most common solicited systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups. Within each group there was a slight tendency towards a decrease in the percentage of subjects reporting solicited reactions after the second injection compared with the first injection. Fever (defined as axillary temperature ≥38°C) was reported by a similar percentage of subjects in both vaccine groups both after the first and second injections (3% Agrippal after both injections and 2% to 3% Fluvirin, after first and second injection). No subjects reported body temperature ≥ 40°C.

The percentages of subjects with nonsolicited AEs were similar between the groups (15% and 7% Agrippal vs. 11% and 6% Fluvirin, after first and second injection, respectively).

No death or AE leading to a subject's withdrawal from the study was reported during the study.

There were six subjects who reported six SAEs. (See Table 6, below)

4. Serious Adverse Events – All Cohorts
No particular pattern was observed by cohort, by preferred term or by time of onset

Table 6: Serious Adverse Events by Age Cohort – V71P5

Cohort	Subj. No.	Vaccine Group	Preferred Term	Onset	Duration (Days)	Outcome	Hospitalized
3-8 yrs.	11/1125	Agrippal	Asthmatic Crisis	D18	8	Recovered	Y
	13/1045	Agrippal	Eye Injury	D6	199	Alive w/ sequelae	Y
	11/1073	Fluvirin	Encephalitis	D181	2	Recovered	Y
	11/1081	Fluvirin	Pneumonia	D105	13	Recovered	Y
	11/1203	Fluvirin	Vomiting	D157	4	Recovered	Y
	13/1026	Agrippal	Urinary Tract Infection	D83	10	Recovered	Y
9-17 yrs.	12/2122	Agrippal	Appendicitis	D20	2	Recovered	Y
	11/2047	Agrippal	Renal Colic	D77	13	Recovered	Y
	12/2003	Agrippal	Appendicitis	D153	23	Recovered	Y
	12/2146	Agrippal	Vomiting	D178	1	Recovered	Y
18-64 yrs.	21/3015	Agrippal	Diverticulitis	D138	5	Recovered	Y
	21/3028	Agrippal	Appendicitis	D99	1	Recovered	Y
	21/3038	Fluvirin	Syncope	D103	<1	Recovered	Y
	21/3099	Agrippal	Visual Acuity Reduced Transiently	D42	7	Recovered	Y
	21/3360	Fluvirin	Gastritis	D149	4	Recovered	Y
	21/3383	Agrippal	Dysentery	D70	12	Recovered	Y
	21/3457	Agrippal	Abortion Spontaneous	D60	<1	Recovered	N
	21/3519	Agrippal	Ovarian Epithelial Cancer	D91		Recovered	Y
STN 125287, V71P5 Clinical Study Report, Table 12.3.1.2-1							

5. Pregnancies
Pregnancy was reported in 7 subjects, 3 of whom were lost to follow-up. One spontaneous abortion was reported at estimated 14 weeks gestation.

2.2.2 Supporting Studies

In addition to the pivotal studies, a total of 1702 adults, aged 18-64 years and 946 adults, aged ≥ 65 years, have received IVV in various controlled and uncontrolled clinical studies, including active controlled, randomized studies which 1012 adults and 483 adults received IVV, in the respective age groups.

Studies have evaluated booster shots in 1131 subjects (469 adults aged ≥ 65 years) following IVV or another influenza vaccination.

Eight supporting studies have evaluated IVV in geriatric populations, many are uncontrolled.

A single study, V58P4E1 is referenced by the sponsor as an evaluation of the safety of IVV re-vaccination in older adults, but the study was actually designed to compare an investigational cell culture-derived influenza vaccine to IVV. The safety data analyses are limited to descriptive.

2.2.3. Limitations of Clinical Studies

The non-pivotal studies did not use a US-licensed comparator. Although there is no a priori reason to suspect that study results following vaccination with a non-US licensed product would significantly differ from those obtained using US licensed products, it should be noted that all

submitted comparator studies and the repeat vaccination study all involved a cell-culture derived influenza vaccine comparator. It is not clear how the safety of such a product would compare to US licensed influenza vaccines.

Subjects were followed more intensely, using diary cards, for the several days immediately post-vaccination in the supporting studies, and only spontaneously reported AEs were collected following that, e.g., up to 3 weeks post-vaccination or up to 6 months post-vaccination.

Pediatric subjects
Relatively limited safety data are available from children and adolescents, based upon a total of 802 subjects (50% between 3-8 years of age, and 50% between 9-17 years of age. No particular safety signal has been identified in this age group or in informal comparisons to adults. An additional pediatric study is planned for 2008/2009 (V71P7) and a pediatric indication is not being sought at this time.

Re-vaccination
A single study, V58P4E1, is reported to have evaluated a second influenza immunization at one year following the first immunization. This study enrolled adults, including elderly and compared IVV to a cell culture derived influenza vaccine. Only those AEs deemed possibly or probably related to vaccination were reported and occurred in ≤1% of subjects. There is no description of an overall safety comparison between the two vaccination groups.

Concomitant vaccination
V58P4E2 is ongoing to evaluate the effect of concomitant polysaccharide pneumococcal vaccine in the elderly. This application does not describe any other data or studies in subjects receiving concomitant vaccination.

a. Populations not specifically studied in the pre-approval phase.

- Pregnant or lactating women
    - V71P5 and V71P6 report 18 pregnancies in 17 female subjects, 15 of whom were exposed to IVV. Of 7 pregnancies in V71P5, 3 resulted in live births. Two cases of spontaneous abortion were reported at around 2 months post-vaccination.
    - Four females from supporting studies are reported to have become pregnant during 6-month follow-up. Three subjects were reported to have delivered healthy newborns with no congenital anomalies and the fourth subject was lost to follow-up and her pregnancy outcome is unknown.
    - The sponsor will attempt post-market follow-up of all women who receive IVV during pregnancy, to include pregnancy course and outcome.

- Individuals with common co-morbid conditions
    - 2006-2007 season study (not further identified) of 361 “at risk” adults 18-60 years of age (circulatory system, diabetes and chronic respiratory conditions), including 180 who received IVV. No safety signal was reported.

- Immunocompromised individuals
    - Previous studies of a thimerosal-containing formulation of IVV were evaluated in renal transplant patients. No safety signal was reported.

- Very elderly / frail elderly

- No data are provided regarding safety in very elderly / frail elderly.
- Adult subjects in the two submitted studies are relatively young, mean ages 31 years and 38 years, respectively.
- A three-season study of 150,000 subjects comparing at least 75,000 IVV recipients to recipients of an adjuvanted-influenza vaccine was initiated in Italy in 2006 (C7OP1). The study will evaluate risk of hospitalization for allergic reactions, convulsions, Guillain-Barré, thrombocytopenia, encephalomyelitis, neuritis and vasculitis.

c. Adverse events

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Post-marketing AE Reports

Standardized MedDRA Queries were used to monitor for AEs of special interest with respect to influenza vaccination.

Table 2: Cases of Interest Identified Using MedDRA SMQs

# Reports	SMQ	Comments
16	Anaphylactic reactions	No confirmed IgE-mediated anaphylaxis
43	Angioedema	Most of the cases report urticaria
9	Convulsions	Both febrile and afebrile convulsions are reported
20	Guillain-Barré Syndrome	Onset days - 11 wks postvaccination; no case definition
11	Hematopoietic cytopenias	Thrombocytopenia in all reports, but one (neutropenia)
1	Haemolytic disorders	Haemolytic anemia one day after vaccination
8	Lack of efficacy / effect	Clinical diagnosis and influenza infection not confirmed by laboratory examinations in most cases
7	Non-infectious encephalitis	One case of postvaccinal myelitis; two cases of acute disseminated encephalomyelitis
25	Peripheral neuropathy	Cases of GBS and isolated cases of neuritis/neuralgia
From BLA 125297, Appendix 1.16, page 4, Table 1		

d. Potential interactions

No potential food-drug or drug-drug interactions have been reported in prospective clinical studies of influenza vaccination.

A literature report (Paliani 2003) reported an interaction between influenza vaccine and anticoagulation (increased international normalized ratio or INR) during the 2001-2002 season. Various studies have reported reduced, unchanged or increased INR following influenza vaccination, however a randomized, blinded, placebo cross-over study of 104 individuals on stable, long-term, oral anticoagulant therapy showed no statistically relevant interactions between vaccination and oral anticoagulant therapy (Ioria 2006).

2.2 Summary

No specific safety signals were identified in the submitted studies.

3.1 Summary of ongoing safety issues

Important identified risks

Allergies and sensitivities to components of the vaccine

Important potential risks

No potential risks are identified from these study data.

Ongoing pharmacovigilance is/will be used to monitor adverse events of interest (Refer to review of safety labeling, above)

Important Missing Information
No missing information is identified, but note that this reviewer was not involved prior to submission of this BLA.

3.1.2 Routine pharmacovigilance practices
A Pharmacovigilance system has been established by Novartis Vaccines and Diagnostics to adequately fulfill regulatory requirements worldwide. This includes use of a variety of signal detection tools.

Expedited reporting is conducted in compliance with regulatory reporting requirements.

Periodic Safety Reports will be compiled in accordance with applicable legislation to provide continuous overview of the safety profile of IVV once licensed

3.1.3 Action plans for specific safety concerns
No risk minimization plan or activities are proposed by the sponsor.

Request for any specific post-marketing monitoring activities will be based upon those concerns raised by the clinical, CMC and statistical reviews.

3.1.4 Summary of actions, including milestones
The sponsor concludes that there are no significant new risks with use of IVV, and no recommendation for change in current product information, and no specific pharmacovigilance plan is proposed in association with U.S. licensure of the product.

Enhanced reporting is conducted for pregnancy and lactation in females exposed to IVV.

3.2 Pharmacovigilance methods
No specific IVV partmarketing activities are proposed.

STN 125279, Appendix 1.16 summarizes the general structure and function of the sponsor's Pharmacovigilance system.

Novartis database utilizes ----b(4)---------- software provided by -b(4)----------
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Novartis Vaccines Pharmacovigilance group

- Handles all post-marketing safety reports
- Implements signal detection strategies and quality control
- Creates Periodic Safety Update Report updates (PSURs)
- Works with Novartis Vaccine Development applications group to upgrade and validate the safety database system
- Responds to regulatory authority requests, e.g., for labeling updates.

COMMENTS:
(Questions for the sponsor and additional recommendations and requests are bolded)

1. Adverse events typically reported after influenza vaccination e.g., injection-site reactions, fever, headache, malaise, are reported at similar rates of frequency and severity for IVV and US-licensed Fluvrin in the pivotal studies.

2. According to the sponsor, less common AE of interest reported after influenza vaccination, e.g., thrombocytopenia, anaphylactic reaction, vasculitis, acute disseminated encephalomyelitis (ADEM) or Guillain-Barré Syndrome were not reported in IVV clinical trials to date, although such events are expected to be reported following wide-spread use of the product post-licensure. .

3. Standard MedDRA Queries were used to evaluate existing post-marketing data for less common AE of interest, e.g., anaphylactic reactions, angioedema, convulsions, Guillain-Barré Syndrome, hematopoietic cytopenias, haemolytic disorders, lack of efficacy / effect, non-infectious encephalitis and peripheral neuropathy. These events were rarely reported and only limited information is available in many cases, as would be expected.

4. Limitations of studies V71P5 and V71P6 submitted to directly support licensure:

    a. These 2 studies were conducted outside the US and had relatively few Black subjects, none and 2%, respectively. There are no known or a priori reasons to suspect that the safety of IVV, or influenza vaccines in general, differs between Caucasians and Blacks or other ethnic/racial groups, however, this issue should be evaluated in subsequent studies or monitored in post-marketing studies.

    b. It is not clear how potential cultural, socioeconomic, healthcare access, vaccination history and educational differences between US and the study counties (The Dominican Republic and Brazil), as well as the particular populations studied might impact on reporting rates in these non-US studies.

    c. Why did the 3-8 and 9-17 year old cohorts in Study V71P5 enroll only Caucasian subjects, while the 18-64 year old cohort enrolled 21% Hispanic and 79% Caucasian subjects?

5. The evaluation of safety and evaluation of risk to benefit is inadequate in older adults.

    a. The mean age of adult study subjects was 31 years in V71P5 and 38 years in V71P6.

    b. While C70P1 will study up to 150,000 elderly individuals, 75,000 of whom will receive IVV and 75,000 of whom will receive an unlicensed, adjuvanted influenza vaccine, it is unclear what thresholds have been prospectively identified to determine safety in the IVV group. It appears that the focus of this study is to demonstrate safety of the unlicensed, adjuvanted product including hospitalization for various AEs thought to be potentially related to the adjuvanted vaccine. The sponsor should describe whether safety data on IVV recipients from this study will provide anything more than descriptive safety data.

    c. The sponsor should provide a time frame for submission of clinical study report for Study V58P4E2 which will evaluate the effect of concomitant polysaccharide pneumococcal vaccine in the elderly, and is reported as ongoing.

6. Safety data in pediatric populations are limited. The sponsor has acknowledged this, is not seeking an indication in the pediatric population and plans to conduct additional studies in the future.

7. **The sponsor should provide final follow-up on the outcomes of the all pregnancies that occurred in studies V71P5 and V71P6.**

8. **With respect to enhanced surveillance, the sponsor should provide a comprehensive list of all such events of interest for Agrippal, and indicate the time frame for submission of these additional data to FDA.**

9. **The sponsor should be asked to submit a Pharmacovigilance Plan at the time of submission of the final reports for clinical efficacy study/studies, incorporating any safety signals identified. This should also include safety signals identified in the review of clinical studies submitted in this BLA.**

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