Summary Basis of Regulatory Action

Date: November 25, 2009

From: Anissa Cheung, M.Sc., Chair of the Review Committee

BLA/ STN#: 125297/0

Applicant Name: Novartis Vaccines and Diagnostics, Inc.

Date of Submission: July 10, 2008

Complete Response Letter Issued: April 27, 2009

Date of Re-submission: May 29, 2009

PDUFA Goal Date: November 28, 2009

Proprietary Name: AGRIFLU

Established Name: Influenza Virus Vaccine, Inactivated

Indication: AGRIFLU is indicated for use in persons 18 years of age or older, for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Norman Baylor, Ph.D., Director, Office of Vaccine Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Melisse Baylor, MD – 11/09
Statistical Review	Tsai-Lien Lin, Ph.D. – 7/08, 1/09, 10/09
CMC Review	Ira Berkower, MD/Ph.D. – 10/7/09, 10/14/09
Testing Method and Analytical Chemistry Review	Rajesh Gupta, Ph.D. – 3/09, 5/09, 7/09, 10/09

Pharmacology/ Toxicology Review	Martin Green, Ph.D. – 3/09 Marion Gruber, Ph.D. – 11/08, 1/09, 5/09
Bioresearch Monitoring Review	Robert Wesley, B.Sc. – 3/09
Establishment Inspection Report	Rebecca Olin, RN – 4/09, 7/09, 10/09, 11/09 Anissa Cheung, M.Sc. – 6/09, 10/09
Post Marketing Surveillance	Patricia Rohan, MD – 2/09
Advertising and Promotional Labeling	Lisa Stockbridge, Ph.D.- 1/09, 2/09, 5/09, 10/09

1. Introduction

Novartis Vaccines and Diagnostics, Inc. submitted Biologics License Application (BLA) 125297 on July 10, 2008. This BLA is a request for licensure of an inactivated influenza virus surface antigen vaccine, AGRIPPAL, for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. This BLA included data on product development and characterization, manufacturing process validation and details of all in-process and quality control testing to ensure the safety, purity, and potency of the product intended for release to market. In addition, this BLA included pre-clinical and clinical data to support the efficacy and safety of the product. On March 13, 2009 Novartis submitted an amendment to this BLA to request a change in the proposed proprietary name from AGRIPPAL to AGRIFLU. According to Novartis, AGRIFLU will create less confusion with other licensed influenza vaccines in the US that also have the letters "FLU" in their names. The Advertising and Promotional Labeling Branch recommended approval of the proposed proprietary name AGRIFLU. A complete response letter was sent to the sponsor on April 27, 2009. Additional information requested in this letter was related to all aspects of the review, but the critical requests were related to the assessment of product safety and potency. The sponsor submitted a full response to the complete response letter on May 29, 2009.

This document includes summaries of each of the major review disciplines associated with the review of this BLA and highlights the major issues covered and brought to resolution during the review process for AGRIFLU. These include:

- An assessment of viral inactivation in vaccine manufacturing.
- The validity of the ---b(4)--------- model for the -b(4)-- assay used to determine vaccine potency.
- Insufficient information provided for the manufacturing facility in the original submission.
- The high mortality of pups observed in both reproductive toxicity studies, b(4)000-40 and b(4)000-43.

2. Background

AGRIPPAL was first licensed in Italy in 1986 and is now licensed for use in more than 50 countries worldwide. The initial formulation of AGRIPPAL contained thimerosal as a preservative. The sponsor subsequently began producing a thimerosal-free formulation in 2003. According to the sponsor, more than ---b(4)----- -- doses have been distributed worldwide including more than --b(4)--doses of the thimerosal-free formulation; the presentation for which the sponsor is applying for licensure in the U.S.

Novartis first submitted an IND -b(4)- for AGRIPPAL on February 20, 2007. At that time, CBER agreed that the sponsor could use the hemagglutinin inhibiting antibodies (HAI) titers as a surrogate endpoint for efficacy to support the accelerated approval of their vaccine. The regulations for accelerated approval specify that applicants are required to conduct an adequate and well-controlled study to confirm the clinical benefit of the vaccine. After the BLA submission, Novartis proposed to change their proprietary name to AGRIFLU in March, 2009.

AGRIFLU is an inactivated, trivalent, influenza virus surface antigen vaccine consisting of three monovalent pooled harvests of --b(4)----, inactivated influenza A types H1N1 and H3N2, and influenza B, produced in embryonated eggs. Each monovalent pooled harvest is a --b(4)-- suspension containing predominantly the purified outer membrane proteins, Hemagglutinin and Neuraminidase, from a single influenza virus vaccine strain. Representative influenza A and B strains are defined annually and are obtained from a qualified World Health Organization (WHO) laboratory.

One dose of AGRIFLU is formulated to contain 15 µg of influenza virus hemagglutinin (HA) from each of the influenza A types (H1N1 and H3N2) and influenza B. The vaccine does not contain preservative and is available as a 0.5 mL single-dose, pre-filled, ---b(4)------ disposable syringe. The proposed shelf life is 12 months at 2-8^{0}C and the date of manufacturing starts from the filling date of the final container.

This vaccine is intended for use in persons 18 years of age or older.

3. Chemistry Manufacturing and Controls (CMC)

Place of Manufacture: The vaccine is manufactured at two locations:

Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina 1
53100 Siena
Italy

Novartis Vaccines and Diagnostics S.r.l
----b(4)-------
----------b(4)---------
-b(4)--

The manufacturing process for the production of this inactivated, subunit influenza virus antigen vaccine is based on the inoculation of embryonated eggs with the influenza virus strains recommended on a yearly basis by WHO and FDA's Vaccines and Related Biological Products Advisory Committee. The monovalent pools are manufactured at the Siena, Italy location. Virus is inoculated into the allantoic cavity of eggs, and after incubation, the allantoic fluid is then harvested, clarified, ultrafiltered, and concentrated in preparation for virus inactivation. Virus inactivation is accomplished by exposure to formaldehyde. The formaldehyde inactivated virus is purified by --------b(4)----------
----------and the detergent, CTAB, --------b(4)----------, hemagglutinin and neuraminidase, from the ----------b(4)----------
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Final drug product formulation is a blend of hemagglutinin antigens (HA) from the two influenza A types and one influenza B virus strains, plus the excipients consisting of --------b(4)----------
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----------. The trivalent vaccine bulk is then filled into 0.5 mL single-dose, pre-filled, -b(4)-- disposable syringes at the ---b(4)---------- site. Stability data is included in the submission to support the requested shelf life for final product for 12 months at 2-8^{0}C and the date of manufacturing starts from the filling date of the final container.

a) Product Quality – Critical elements of the product information included in the BLA are related to the inactivation of the influenza virus, determination of the HA potency for formulation, validation of the manufacturing process for the final vaccine product, development of appropriate quality control testing plan to ensure manufacturing consistency and final container product quality, and stability data to support the hold times for intermediates and bulks, and to support the requested shelf life for the product once released for market distribution. Data and information included in the BLA demonstrate that the manufacturing process is well controlled. Details below represent some of the critical aspects of the product review.

Inactivation of influenza virus: Virus inactivation is one of the key manufacturing steps that need to be optimized for the new influenza virus strains each year. The ----------b(4)----------. In the original BLA submission, the specification for the inactivation --b(4)---------- ranged from ----b(4)---------- for a minimum of --b(4)--. However, data from the H3N2 (X161B) strain for the 2007/8 season showed that a -------b(4)---------- and duration of --b(4)---- is required for the complete inactivation as demonstrated by the absence of live virus at the last b(4) time points. In response to the observed resistance in virus inactivation, the sponsor changed the inactivation ----------b(4)----------. In the information request of December 8, 2008, CBER asked the sponsor to provide a protocol to show the schematic plan on how to inactivate influenza virus strains that -b(4)----- to inactivation by formaldehyde under these conditions. The sponsor submitted their proposed inactivation protocol on February 18, 2009 under Amendment 5. The optimized inactivation condition for each influenza virus strain is determined initially by a small scale study, followed by validation with -b(4)- full scale production lots. If the validation lot results fail to meet the acceptance criterion ----- ------b(4)------ ---------- -------. The sponsor proposed that -----b(4)---------- is the final condition that will be used for the influenza virus strains ---b(4)---------- to formaldehyde inactivation. The sponsor included data in the BLA to demonstrate that complete virus inactivation proceeds much ----------b(4)---------- without any significant impact on the HA potency of the -----b(4)---------- as measured by -b(4)- assay. The CMC reviewer agrees that the inactivation protocol is acceptable; however, there was concern that ----------b(4)---------- may have some detrimental effects on the key antigenic determinants on hemagglutinin. The final conclusion from the Division of Viral Products is that the manufacturer has a validated potency assay -b(4)--- that is acceptable for quality control of inactivated influenza vaccines. In addition, the manufacturer has submitted adequate data to support that the inactivation -------b(4)------ for a maximum of -b(4)---------- has no significant impact on the potency of the vaccine product. Novartis commits to submit results of the on-going stability studies of the -----b(4)---------- ----------. The final stability report will be submitted in January 2010.

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----------b(4)----------

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Product Stability and Shelf Life - Stability data for the storage of each intermediate and final container are supportive of the stability of the product at each stage of the manufacturing process. This includes data for ----------b(4)----------
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and final container drug product storage for 12 months at 2 – 8°C.

Clinical Assays – The CMC review of this file also included a review of the relevant clinical assay used to measure the immune status of trial participants at the time of entry into the clinical studies and post immunization. Hemagglutination Inhibition assay (HAI) was used by the sponsor to detect hemagglutinin inhibiting antibodies in serum samples from trial participants. The HAI assay used for the evaluation of clinical trial specimens was adequately validated and was performed using appropriate controls.

b) CBER Lot Release – A lot release protocol for the formulated trivalent bulk was submitted to the BLA, and includes all the release tests performed on the formulated trivalent bulk and each monovalent pooled harvest constituted the formulated bulk. Samples and the results of ---b(4)--------- test of at least three, but not more than five lots of monovalent pooled harvests from each of the 3 strains of influenza virus will be submitted to CBER for testing at the beginning of each new influenza season. CBER will only release the formulated trivalent bulk lots for AGRIFLU. Samples and final protocols for the formulated trivalent bulks will be submitted to CBER for lot release. The final lot release protocol template for the formulated trivalent bulk was submitted to CBER for review on November 23, 2009 under Amendment 24. The sponsor accepted all the requested changes from CBER in the format of the lot release protocol for the formulated trivalent bulk. The sponsor committed to incorporate the minor changes on the -b(4)- reporting to the lot release protocol and the associated SOPs for the next influenza season (2010-2011) as a post-approval submission.

All testing will be performed in OVRR/DPQ.

c) Facilities review/inspection – The Complete Response Letter issued on April 27, 2009 included a range of facility issues such as the lack of information for the --b(4)---------- filters used in the manufacturing process, absence of media fill validation data, insufficient data on the validation report for the syringe filling process for Filling Machine -b(4)----, insufficient information provided in the validation report of the Inspection Machine --b(4)----, no information submitted for the ----b(4)-------- and no reference to a -b(4)---- step for the syringe -b(4)- for filling line --b(4)---. On May 29, 2009, Novartis responded to the Complete Response letter. Review of the firm's response generated additional questions which were conveyed to the firm on August 18, 2009. The firm responded to these questions on October 13, 2009 under

Amendment 22. The facility reviewer agrees that the sponsor's final responses adequately addressed all facility issues.

An inspection of the manufacturing and filling facilities was conducted from February 5-13, 2009. The facilities inspected were:

Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina 1
53100 Siena, Italy
FEI # 3007780504

Novartis Vaccines and Diagnostics S.r.l.
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---b(4)----------
-b(4)-
--------b(4)-----------

The Siena site is where the ----b(4)----------- and the -------b(4)---------- are manufactured, while the -b(4)- site is where the ----------b(4)---------- ----------. In-process and release testing of the monovalent pooled harvests, formulated trivalent bulks, and final drug product are ----b(4)----------. Overall, these facilities were considered to be within compliance and all processes were well controlled. This inspection concluded with the presentation of a 483 containing five items. Findings included: no data to support a -b(4)--- hold time for the --------b(4)----------; the validation to support a --b(4)--- hold time for the ----b(4)----------was not conducted under an approved protocol; the batch record did not reflect the actual practice in the firm; the cleaning procedure for the inoculation machine has not been properly validated; and there are no procedures in place to assure an urgent change request enters the Change Control Systems in a timely manner. All items in the 483 were appropriately addressed by the sponsor (detailed in amendments 14 and 16 submitted to the BLA) and the compliance status of this site is deemed acceptable for product approval.

b) Environmental Assessment - A request for a categorical exclusion from an Environmental Assessment under 21 CFR § 25.31(c) was submitted to the BLA. It was concluded that the request was justified as the product is composed of naturally occurring substances and that no extraordinary circumstances exist, which would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Two toxicology studies were performed on the final vaccine formulation, and these studies were important for demonstrating the initial safety of the vaccine.

Two separate reviewers were involved in evaluating the preclinical studies performed on this product. These reviewers provided reviews on:

- Repeat dose intramuscular toxicity study of the final vaccine formulation in --b(4)--------white rabbits.
- Reproductive toxicity studies of the final vaccine formulation in rabbits.

Summary of repeat dose intramuscular toxicity study performed using final product vaccine: A repeat dose toxicity study on the final vaccine was carried out in ----b(4)----- rabbits. Rabbits were given 2 intramuscular injections of human dosage (45 µg HA), 7 days apart, in the study. The results from this study showed that the vaccine was well tolerated, and no consistent signs of systemic toxicity were observed. Injection site inflammation remained local and showed signs of resolution. The conclusion of this study was no observation of adverse gross or microscopic alternations that would indicate an unacceptable systemic or local toxicity related to vaccine treatment.

Summary of Reproductive toxicity studies: This vaccine will be administered to a target population that includes females of childbearing age; therefore toxicity studies related to reproduction were also conducted. The sponsor performed 2 studies (b(4)000-40 and b(4)000-43) to evaluate the reproductive and developmental toxicity potential of the final vaccine in rabbits, including a postnatal evaluation. In study b(4)000-40, animals were dosed on study days 1, 15, and 29 prior to mating and on gestation days 7 and 20 either with the AGRIFLU vaccine, 0.5 mL, I.M., 45 µg antigen or saline control. Animals were divided into subgroups and either underwent Caesarean section on gestation day 29 or were allowed to rear their offspring. Data from animals assigned to the Caesarean section group suggested that the vaccine has no effects on mating, fertility, pregnancy, and embryo-fetal development. However, high pup mortality in the natural delivery subgroups in both, vaccine and saline control treated group, did not allow a meaningful assessment of development endpoints of the F1 generation. The sponsor did perform an investigation to evaluate the cause of the observed high pup mortality and attributed it to the handling of the pups during lactation days 1-5. A second study --b(4)-000-43 was conducted. As in study -b(4)000-40, there were insufficient numbers of evaluable litters to allow a post-natal assessment due to high pup mortality in both, the vaccine and saline control treated groups.

The reviewer did not consider the observed pup death to be a vaccine related effect, as it occurred in both, vaccine and control groups, but rather, a result of coincidental stress that the does underwent while on study. However, the observed postnatal pup deaths that occurred in both, the initial study b(4)000-40 (42.6% in control and 50.5% in the vaccine group) and in the repeat study b(4)000-43 (46.9% in control and 36.4% in vaccine group) did not allow a meaningful postnatal assessment of the F1 generation. Thus, the labeling will state that post-natal development of the F1 generation could not be fully evaluated.

In conclusion, the toxicology studies performed in rabbits showed that AGRIFLU is safe in this animal model. The vaccine did not demonstrate signs of systemic and local toxicity. The vaccine exerts no adverse effects on mating, fertility, pregnancy, embryo-fetal development, and there was absence of vaccine-related teratogenic effects. However, potential vaccine related effects on post-natal development could not be fully evaluated.

5. Clinical Pharmacology

The immune response elicited by the vaccine is measured by assaying for the presence of hemagglutinin inhibiting antibodies (HAI) for each type of influenza virus in the serum of vaccinated individuals three weeks after vaccination (Day 21). The immunogenicity of AGRIFLU in the two clinical pivotal studies was assessed by endpoints and criteria described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." The two endpoints were: 1) proportion of subjects with seroconversion (four fold rise in HAI titers or change from undetectable to a titer of ≥ 1:40) at Day 21 for all three hemagglutinin antigens and 2) proportion of subjects achieving a HAI titer ≥ 1:40 at 3 weeks following vaccination for each of the three hemagglutinin antigens. The criteria for demonstration of immunogenicity are the lower bound 95% confidence interval for percentage of subjects having seroconversion of ≥ 40%, and the percentage of subjects achieving HAI titers ≥ 1:40 at 21 days post-vaccination of ≥ 70%.

6. Clinical/ Statistical

Accelerated approval of AGRIFLU is based on immunogenicity and safety data from studies using a surrogate endpoint (HAI titers) for clinical efficacy. Results discussed in this section are based on both the clinical and statistical reviews submitted to the file. The clinical studies conducted to demonstrate the efficacy and safety of this product, and to support the licensure of this vaccine involved two pivotal efficacy trials (V71P5 and V71P6), three additional studies to support immunogenicity, and 11 additional trials to support safety. Each of these study protocols and study outcomes are detailed in the BLA and are covered in the clinical review. It was the conclusion of both clinical and statistical reviewers that the data presented support the recommendation for approval of this vaccine. Included in this report is a summary of the findings of the clinical and statistical reviewers for the efficacy and safety studies (summarized in section 7 of this report).

a) Clinical Program -

Efficacy –The first pivotal trial, Study V71P5, was a phase III, observer-blind, randomized, controlled study to evaluate safety, tolerability, and immunogenicity of two trivalent subunit inactivated influenza vaccines (AGRIFLU and Fluvirin) in 1893 healthy subjects aged 3-64 years. Subjects were stratified by age group, and randomized in 2:1 ratio to AGRIFLU or Fluvirin (control). Fluvirin, also manufactured by Novartis, is a trivalent inactivated influenza vaccine licensed in the US for use in persons 4 years of age

and older. A total of 601 healthy children aged 3 to 8 years, 600 healthy children/adolescents aged 9 to 17 years and 692 healthy adults aged 18-64 years were enrolled in this study. The primary objective was to evaluate immunogenicity, measured by percentage of subjects achieving a HAI titer ≥ 1:40 and by percentage of subjects achieving seroconversion in healthy adults aged 18-64 years after a single, 0.5 mL intramuscular dose of AGRIFLU. The second pivotal trial, Study V71P6, was a phase III, randomized, controlled, observer-blind study to evaluate the consistency of three consecutive lots of AGRIFLU, with respect to immunogenicity, in healthy subjects aged 18-49 years. The primary objective was to demonstrate the immunogenic equivalence of three consecutive production lots of AGRIFLU given to healthy adults aged 18-49 years. A total of 1507 subjects were randomized at a 2:2:2:1 ratio to receive AGRIFLU from one of the three consecutive lots or to receive Fluvirin (control). The active control included in the two pivotal studies was intended to provide a comparative assessment for safety only, not for primary immunogenicity comparisons. HAI antibody results for the two clinical trials are shown in the following table.

Table: Hemagglutination-Inhibiting (HAI) Antibody Responses to AGRIFLU in the Two Pivotal Clinical Trials

	V71P5 (N=424) Ages 18-64 years			**V71P6 (N=1182) Ages 18-49 years**		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Seroconversion Rate	74%	72%	77%	94%	67%	84%
LL 95%CI*	69%	68%	72%	93%	65%	82%
% of Subjects with HI≥1:40 Post-Vaccination	93%	96%	91%	98%	99%	87%
LL 95%CI*	90%	94%	87%	97%	98%	85%

*LL 95% CI is the lower limit of the 95% confidence interval.
Source: BLA 125297, CSRs, Table 11.4.1.1-1, page 66 and Table 11.4.1.2.1-1, page 50

The results for the two pivotal studies showed that AGRIFLU met the accelerated approval criteria for demonstration of immunogenicity as described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." Specifically, the lower bound of the 95% confidence interval for the proportion of subjects with seroconversion was greater than 40% for all three strains and the percentage of subjects with HAI titers ≥ 1:40 or higher post-vaccination was greater than 70% for all three strains. The lot-to-lot consistency for three lots of AGRIFLU was demonstrated in pivotal study V71P6. The 95% confidence interval for all pair wise GMT ratios among the three lots range from 0.76 to 1.33, and are within the acceptable range of 0.67 to 1.5.

The three clinical studies (V58P4, V58P9, and V58P2 submitted in support of immunogenicity enrolled 4077 healthy adult volunteers aged 18 years or older. All three of these trials were randomized, observer-blind studies in which AGRIFLU was the active control for an experimental cell-derived seasonal influenza vaccine, also manufactured by

Novartis. These studies were designed to satisfy the yearly criteria for strain changes as recommended by Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA). As shown in the table below, the results of two of these studies satisfied both the criteria recommend by the CPMP and those recommended by CBER.

Table: Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers in Supportive Immunogenicity Studies of AGRIFLU (Studies V58P4 and V58P9)

	18-60 Years of Age		**≥61 Years of Age**
	V58P4 N=644	**V58P9 N=168**	**V58P4 N=674**
Seroconversion Rate			
H1N1	67% (63%)	77% (70%)	55% (51%)
H3N2	64% (60%)	88% (82%)	65% (61%)
B	81% (78%)	70% (63%)	73% (70%)
Post-Vaccination % of Subjects with HI Titers≥1:40			
H1N1	92% (89%)	95% (91%)	85% (82%)
H3N2	99% (98%)	96% (92%)	98% (97%)
B	91% (88%)	88% (82%)	89% (87%)

Source: BLA 125297, CSR, Tables 11.4.1.1-1 – 14.1.1.-3 and 11.4.1.2-1 – 1.4.1.2-3 pages 80-85, and Tables 11.4.1-2 – 14.1-4 pages 72-76

In these two supportive studies, V58P4 and V58P9, the results for the percentage of subjects with seroconversion and the percentage of subjects with HI titers of 1:40 or greater after vaccination with AGRIFLU met the target CBER criteria for accelerated approval for both influenza A subtypes and for the influenza B type.

The results of a third study, V58P2 were submitted at the request of CBER. This study was similar in design to Study V58P4, but was a smaller study conducted in a study population in which a large percentage of subjects had been vaccinated previously against influenza.

The seroconversion rate for all three strains and in both age groups did not meet the criteria described in the FDA Guidance for Industry. The percentage of subjects with post-vaccination titers of 1:40 or higher did meet the criteria for the influenza A/H3N2 strain in both age groups, but not for the other two influenza strains. The reason for the poor outcome in this study was unclear but may be related to a high percentage of subjects with pre-existing antibody titers. It must be noted that this study was designed to satisfy criteria used by the EMEA and was not designed to support licensure in the United States.

In the opinion of both the clinical and statistical reviewers, the HAI antibody results from the two pivotal studies (V71P5 and V71P6) and the two supportive studies (V58P4 and V58P9) support the effectiveness of AGRIFLU.

Results of Biomonitoring Review – The BIMO reviewer conducted inspections of two clinical trial sites where pivotal trial V71P6 was conducted. These inspections were classified as voluntary action indicated and both sites were in Santo Domingo, in the Dominican Republique. Overall, the conclusion from the BIMO report is that no issues were identified that would impact interpretations of the clinical data submitted to the BLA to support licensure.

b) PREA – A presentation was made to the FDA Pediatric Review Committee (PeRC) on September 23, 2009. The following recommendations were presented and accepted by the committee, and are included in the approval letter as follows:

We are waiving the pediatric study requirement in infants from 0 to <6 months of age, because the necessary studies are impossible or highly impracticable to conduct and there is evidence strongly suggesting that the product would be ineffective in this age group.

We are deferring submission of the study for ages 6 months to 17 years for this application because this product is ready for approval for use in adults.

The deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below:

1. Novartis Vaccines and Diagnostics agree to conduct Study No. V71_18, a randomized, observer-blind, non-inferiority immunogenicity and safety study with Novartis' AGRIFLU and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 3 years to 17 years of age. The final protocol for this study will be submitted by December 31, 2009. The study will be initiated in September 2010. The final study report will be submitted in January 2012.

2. Novartis Vaccines and Diagnostics agree to conduct Study No. V71_20, a randomized, observer-blind, immunogenicity and safety study with Novartis' AGRIFLU and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 6 months to less than 3 years of age. The final protocol for this study will be submitted by December 31, 2010. The study will be initiated in September 2011. The final study report will be submitted in January 2013.

The final study protocols and reports will be submitted to the BLA.

7. Safety

In support of the safety of AGRIFLU, the sponsor submitted the results from two pivotal studies, V71P5 and V71P6, which were randomized, observer-blind studies comparing AGRIFLU to Fluvirin in healthy adult volunteers. A total of 692 adults from 18 to 64 years of age were randomized and vaccinated in Study V71P5; 1507 adults from 18 to 49 years of age were randomized and vaccinated in study V71P6. Additional support for the safety of AGRIFLU was provided by the safety data from 1) six European annual re-registration studies, 2) three studies comparing thimerosal-free and thimerosal-reduced formulations, 3) the re-vaccination study of subjects in V58P4, and 4) a pilot study conducted at a new study site.

The most commonly observed adverse events in the seven days after vaccination with AGRIFLU were local events. Across all studies of AGRIFLU, pain at the injection site was the most commonly reported solicited adverse reaction and was reported in 22% and 25% in the two pivotal trials. The other solicited adverse events were reported less commonly: induration was reported in 5%-10%, swelling in 4%-6%, erythema in 5%-6%, and ecchymosis in 5%-6% of subjects in the two pivotal trials. The systemic solicited adverse reactions reported in more than 5% of subjects in either pivotal trial were headache (23%-24% of subjects), myalgia (14%-18% of subjects), malaise (12% of subjects in both studies), fatigue (9%-10% of subjects), arthralgia (5%-6% of subjects), and chills (5%-7% of subjects). The safety results of the supportive studies were similar to those of the two pivotal trials.

Information on spontaneous adverse events was reported in all studies of AGRIFLU. The most commonly reported spontaneous AEs were infections, such as nasopharyngitis, rhinitis, and pharyngeal pain, and headache. No events of Guillain-Barré, anaphylaxis, or oculo-respiratory syndrome were reported in these studies.

In clinical studies included in this BLA, there were a total of four deaths in subjects who received AGRIFLU. All deaths were reported in subjects 61 years of age and older. None of these deaths was judged as related to AGRIFLU. All of the causes of death were consistent with illnesses typically seen in elderly individuals.

There were 10 pregnancies in the clinical studies included in this BLA. Four pregnancies ended in spontaneous abortions. One of these was associated with a motor vehicle accident. The number of pregnancies was small; no conclusions can be reached regarding possible vaccine related adverse pregnancy outcomes.

Overall, the adverse events most commonly observed after vaccination with AGRIFLU were local events at the injection site, particularly pain. The most common systemic event was headache. No evidence for an increase in severity or seriousness of adverse events was observed by the clinical reviewer. Therefore the safety profile of AGRIFLU was acceptable for clinical approval of this application.

8. Advisory Committee Meeting

CBER did not present these data to an Advisory Committee because our review of information submitted in the BLA did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issue

No applicable.

10. Labeling

The package insert (PI) originally submitted in the BLA was reviewed by all relevant reviewers on the file. These include the clinical and statistical reviewers, the product reviewers and reviewers from the Advertising and Promotional Labeling Branch. Several rounds of changes were made to the label submitted by the sponsor. Most of these changes were minor.

Based on the reproductive toxicology studies and the safety data from the clinical trials related to pregnancy events, the label will have a statement that this product is classified as pregnancy category B. The label will also state that potential vaccine related effects on post-natal development could not be fully evaluated.

In addition to the package insert, the Advertising and Promotional Labeling Branch reviewed and recommended approval of the proposed proprietary name for this product, the carton and container packaging information, and the logo and pre-product release advertising. After some discussion with the sponsor, all of these submissions were found to be acceptable.

The sponsor will submit the label in Structured Product Labeling (SPL) format after product licensure.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action
Following the review of all supportive product and clinical data, it is the recommendation of the review committee to approve this product for licensure.

b) Risk/ Benefit Assessment
The quality, efficacy, and safety of this vaccine have been thoroughly reviewed and have been determined to be acceptable for use of this vaccine as indicated in the label.

c) Recommendation for Postmarketing Risk Management Activities
There was no recommendation for postmarketing risk management activities. See below for the postmarketing activities associated with the licensure of this product.

d) Recommendation for Postmarketing Activities
Postmarketing activities include studies that will be performed post-licensure. These studies are classified as either postmarketing requirements under Section 505B(a) of the Food Drug and Cosmetic Act (FDCA), postmarketing commitments subject to 21 CFR 601.70. or postmarketing commitments not subject to 21 CFR 601.70. During the review of the BLA, it was determined that a postmarketing study to assess the efficacy and safety of AGRIFLU in the pediatric population was required. The plan and timing for these studies were discussed with Novartis and an agreement was reached on how these studies were to be conducted.

The following postmarketing activities are included in the approval letter:

Postmarketing Requirements under Section 505B(a) of the FDCA:

1. Novartis Vaccines and Diagnostics agree to conduct Study No. V71_18, a randomized, observer-blind, non-inferiority immunogenicity and safety study with Novartis' AGRIFLU and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 3 years to 17 years of age. The final protocol for this study will be submitted by December 31, 2009. The study will be initiated in September 2010. The final study report will be submitted in January 2012.

2. Novartis Vaccines and Diagnostics agree to conduct Study No. V71_20, a randomized, observer-blind, immunogenicity and safety study with Novartis' AGRIFLU and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 6 months to less than 3 years of age. The final protocol for this study will be submitted by December 31, 2010. The study will be initiated in September 2011. The final study report will be submitted in January 2013.

Postmarketing Commitments subject to reporting requirements of 21CFR 601.70.:

3. Novartis Vaccines and Diagnostics agree to submit the results of Study No. V58P13, a placebo-controlled clinical endpoint efficacy and safety study of Novartis' AGRIFLU in healthy adults 18 to 49 years of age. The final study report for the study will be submitted by January 31, 2010.

4. Novartis Vaccines and Diagnostics agree to conduct a non-inferiority immunogenicity study with AGRIFLU and a US-licensed trivalent inactivated seasonal influenza vaccine in a population of adults 50 years of age and older. The final study protocol for this study will be submitted by June 2010. This study will be initiated by March 2013. The final study report will be submitted by November 2014.

5. Novartis Vaccines and Diagnostics agree to establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to AGRIFLU during pregnancy. A protocol for this pregnancy registry will be submitted by June 30, 2010. This protocol will address elements found in FDA's guidance for Industry on Establishing Pregnancy Exposure Registries (9/2/2002) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf). The pregnancy registry will be established by June 30, 2011.