DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852-1448

Our STN: BL **125297/0**

Novartis Vaccines and Diagnostics, Inc.
Attention: Joanne Totosy de Zepetnek
4560 Horton Street
Emeryville, CA 94608-2916

Dear Dr. Totosy de Zepetnek:

We have completed the review of your original biologics license application (BLA) for Influenza Vaccine (Agrippal®) submitted under section 351 of the Public Health Service Act.

Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below:

CMC

1. Additional information is required for a comprehensive assessment of viral inactivation. The inactivation of influenza virus ----------b(4)----------, formaldehyde inactivation ----b(4)----------. Inactivation data for the total virus log reduction --b(4)----------formaldehyde treatment ----b(4)---------- have been provided only for the H3N2 strain. Please provide similar inactivation data for total virus log reduction for influenza H1N1 and B strains. Please also provide a summary table showing the logs of inactivation for the formaldehyde -b(4)-----steps and the sum of logs of inactivation for -b(4)- steps of the manufacturing process.

2. Parts of the manufacturing process have not been completely validated and the following data are still required:

   a. ----------b(4)----------.

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

3. We have the following concerns regarding improper validation of the ----b(4)----- model for the evaluation of the -b(4)- assay used to determine vaccine potency:

   a. An underlying validity assumption of the -b(4)----------assay methodology is the 'similarity' condition.

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

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

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4. Additional information is needed for assessment of the Hemagglutination Inhibition Assay (HAI). The assay validation was described in section 5.3.1.4 study 251875 STF. However, a detailed protocol for the HAI, SOP 101076-04, was not included in the original submission. Please provide the requested protocol.

5. We have the following concerns regarding your viral inactivation test:

   a. You have provided qualification reports for determining the inactivation of influenza virus strains (3.2.S.4.3 [Virus Inactiv] -4 and 3.2.S.4.3 [Viral Inactiv] -4a (Addendum). Both reports are identical except the cover page and line 14 on page 2. Differences in these reports should be distinctly described with a justification for not using all -b(4)-. Please explain in these reports the differences between ---b(4)----------

   b. Though appropriate controls of influenza vaccines used as matrices have included using -b(4)-- eggs, please provide evidence that the vaccine formulations used as matrices have tested negative for residual influenza virus in a test performed according to -b(4)---------- eggs for each passage.

c. Experiments described in the qualification report have been performed at -b(4)- However, the SOP FLU 07.003 (SOP 203564-07) describes incubation of inoculated eggs at b(4) temperatures for trivalent bulk preparations, ----b(4)----------

----b(4)---------- requires incubation of inoculated eggs between -b(4)---------- Please revise the SOP with regard to the incubation temperature that it should not be lower than b(4), to ensure compliance with the -----b(4)---------- and also to be consistent with the qualification study.

6. The documents referred to as containing extractable and leachable data (3.2.P.2.3) for the container closure qualification did not contain this information. Please submit all extractable and leachable studies and data including those conducted according to b(4)-requirements.

7. There are no data in the submission regarding b(4) testing for extractables and leachables for the ---b(4)---------- filters. Please provide data for these studies.

8. Please submit a complete description of the -b(4)-- syringe that will be used for vaccine preparation in the US, including closure integrity and stability data.

FACILITY

9. According to the Quality Risk Analysis of Antigen Filtration for Flu in Building b(4), there are --b(4)---------- filters available for use at the -(b)(4)- filtration step; the --b(4)---------- filters. This document states that the -b(4)- filters are --b(4)-- but no information is provided in support of this claim. Please provide your evaluation of the filters and the data used to conclude that the filters are -b(4)-----

10. In the Quality Risk Assessment, the Batch Record, and the Validation Report for the ----------(b)(4)- Filtration Process the specific type of filter is not identified; however the vendor validation of the -b(4)----filters provided in your submission related to specific filters such as the ----------b(4)----------. Please provide the specific models of ------b(4)--------filters that you are using for ------b(4)---filtration and indicate if the filters are being used ----b(4)----------. If so, please provide your justification in light of the vendors' use of specific strains in their validation reports.

11. The vendor reports for the --b(4)---------- filters are not consistent as to the types of tests or in some cases the depth of testing conducted (see the --b(4)----- extractables testing compared to that of --b(4)-----). Please provide your testing protocol including information as to what specific validation tests were required from the vendor, what worst case testing was required, the acceptance criteria and your evaluation of the study results.

12. Please provide media fill data to support the assurance of sterility ----b(4)---------- ---------- final product.

13. According to Validation Report for the Syringe Filling Process for Filling Machine -b(4)- ---------- reference is made to a dosage verification study conducted on samples taken every --b(4)---. There was no information regarding the purpose of the study and no data were presented to indicate the outcome of the study. Please provide information regarding the study, the test results and study conclusions.

14. Regarding Inspection Machine --b(4)---: The validation information provided was insufficient to conduct a meaningful review. Please provide your validation protocol and final report which should include:

    a. A complete description of the inspection machine;

    b. A description of what --b(4)---------- results mean;

    c. A description of how the validation tests were conducted including a description of test sets, number of runs, acceptance criteria and a discussion of the results and conclusion;

    d. Data to support how the False Reject Rate was calculated and data for the False Accept Rate.

    e. The procedure for the performance test runs conducted ----b(4)---------- ---------- including a description of the test sets.

15. In your submission there was no information or data submitted for the --b(4)---------- used to -b(4)- the stopper bags or the -b(4)- machine used to unpack syringes. Please provide the validation protocol and final reports for these pieces of equipment.

16. There is no reference to a --b(4)-- step for the syringe -b(4)- for filling line --b(4)------ Are the syringe -b(4)- for this line --b(4)-- before they enter the --b(4)---- filling room? If so, please provide the validation of this step. If not, please explain how you control potential contamination from syringe -b(4)- from entering the filling room.

17. There are still outstanding inspectional issues identified in the FDA form 483 (dated February 13, 2009) issued at the conclusion of the pre-licensure inspection of your Siena, Italy location that need to be resolved. You must satisfactorily resolve these issues prior to approval of the application.

CLINICAL

18. We request that you address the following concerns that we have with the Clinical Study Report for V71P5:

    a. Please clarify the difference in subject numbers between the Enrolled population and the Per Protocol population.

        i. For subjects 18-64 years of age and 3-8 years of age, the Enrolled population minus the number of subjects with major protocol violations results in the number of subjects given for the Per Protocol population in Table 11.1-1. However, this does not account for the premature discontinuations listed in Table 10.1-1.

        ii. For subjects 3-8 years of age, the number of major protocol violations is different on page 55 compared to page 60. In addition, adding the number of major protocol violations to the number of subjects excluded from site 14 does not result in the number in the Per Protocol population as provided in Table 11.1-1. The numbers also need to take the premature discontinuations in Table 10.1 into account.

        iii. The Figures on pages 55-57 are not consistent with Tables 10.1 and 11.1-1 or with the text.

    b. Please provide an analysis of immunogenicity by gender.

    c. Please provide an analysis comparing immunogenicity in adults 18-49 years of age and adults 49-64 years of age.

    d. Please provide the criteria used to identify medically significant disease.

    e. Please provide a table of medically significant adverse events with onset at any time during the study.

19. We request that you address the following concerns that we have with the Clinical Study Report for V71P6:

    a. Please reconcile the numbers in the following table so that the numbers of subjects with premature discontinuations or with major protocol violations are consistent with the number of subjects in each study population. (For example, the number vaccinated minus the number of subjects with premature discontinuations does not equal the number making the Day 22 visit).

Table: Study V71P6 - Patient Distribution and Resulting Study Populations

	Lot A	Lot B	Lot C	All Agrippal	Fluvirin
Enrolled	430	431	429	1290	217
Didn't meet entry criteria	5	4	1	10	1
Consent withdrawn	2	1	0	3	0
Vaccinated	423	426	428	1277	216
Received wrong vaccine	1*	2*	4*	2*	3
Consent withdrawn	12	5	12	29	4
Lost to follow-up	10	16	14	40	9
Unknown	1	0	1	2	0
Made Day 22 Visit	400	405	401	1206	203
Major protocol violation	7	9	8	24	8
Per Protocol Population	393	396	393	1182	194
Safety Population	403	404	402	1209	202

b. Please provide an analysis comparing immunogenicity in adults 18-49 years of age and adults 49-64 years of age.

20. Please state the percentage of elderly subjects with pain and erythema (page 121) in the Clinical Study Report for V58P4.

21. Please submit the narratives for all deaths that occurred in studies of Agrippal that were presented in this application.

The proposed proprietary name, Agrippal, has been reviewed and found to be tentatively acceptable. Final acceptability of the name will be determined within 90 days of product approval, when the application is otherwise found acceptable.

We acknowledge that you have included a Pharmacovigilance plan in your BLA; however, we reserve our comments on this proposal for later, when this application is found suitable for approval. Depending on subsequent CBER evaluation and final labeling, CBER may request additions to the Pharmacovigilance plan.

Review and comment on the proposed final labeling will be completed when the application is otherwise acceptable.

We note your intent to submit a supplemental BLA to support the safety and immunogenicity of Agrippal in the pediatric population 3 to 17 years. However, the Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment for all age groups unless a waiver or deferral has been obtained. Please submit your plan for the study of Agrippal in children younger than 3 years of age. This proposal will be formally reviewed by FDA's Pediatric Review Committee prior to final action on the application.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

We acknowledge receipt of your numerous amendment(s) dated August 11, 2008 through April 15, 2009. You may cross reference applicable sections of the amendment(s) in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions, please contact Bernard J.P. McWatters, Ph.D. at (301) 827-3070.

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
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Center for Biologics
Evaluation and Research