

RECORD OF TELEPHONE CONVERSATION

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Product:
Influenza Vaccine, Adjuvanted

Applicant:
Novartis Vaccines and Diagnostics, Inc.

Telecon Date/Time: 18-February-2015 6:56 PM Initiated by FDA? Yes

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Communication Category(ies):
1. Information Request

Author: Theodore Garnett

Telecon Summary:
CBER comments/questions regarding CDISC, clinical, DBSQC and CMC

FDA Participants: Theodore Garnett

Non-FDA Participants: Matthew Gollwitzer

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

From: Garnett, Theodore
Sent: Wednesday, February 18, 2015 6:56 PM
To: matthew.gollwitzer@novartis.com
Subject: STN 125510/0 (FLUAD 65) - New Information Request

Matt,

I have attached new information requests from the review team. Please respond to these requests in a timely manner so we may continue evaluating your BLA.

Thank you!

Ted

Theodore Garnett, Ph.D.

LCDR, U.S. Public Health Service

Microbiologist (Regulatory)

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Our STN: BL 125510/0

Novartis Vaccines and Diagnostics, Inc.
Attention: Mr. Matthew Gollwitzer
350 Massachusetts Ave.
Cambridge, MA 02139

Dear Mr. Gollwitzer:

We are reviewing your biologics license application (BLA) dated November 25, 2014 for Influenza Vaccine, Adjuvanted and have determined that the following information is necessary. Please promptly submit your written response to the following items so that we may continue evaluating your BLA:

CDISC:

1. We note that you did not provide validation results and a Validation and Data Interpretation Report for the CDISC portion of the submission. The validation of the SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) should be reconciled by you prior to submission to ensure errors are resolved or explained as appropriate in the Validation and Data Interpretation Report. Since we did not receive the validation results and report we have performed our own validation and have found the following issues that need to be resolved:
 - a. In Section 5.3.5.1 – V70_27 SDTM had 6 errors, 4 in the VS (Vital Signs) domain and 2 in the RELREC (Related Records) domain – those of concern include:
 - i. RELREC domain - V70_27-109188 AESPID 1 does not exist instead of V70_27-109188 AESPID 2 and 3; and V70_27-326042 AESPID 4 does not exist instead of V70_27-109188 AESPID 1, 2, 3, 5 and 6. Please explain and correct.
 - b. In Section 5.3.5.3 – ISE (Integrated Summary of Efficacy) SDTM had 67804 errors – those of concern include:
 - i. 1259 errors in DM (Demographics) domain. The errors were reported as “Duplicate USUBJID.” The validation rule SD0083 states that “The value of Unique Subject Identifier (USUBJID) variable must be unique for each subject across all trials in the submission.” Please explain and correct the errors.
 - c. In Section 5.3.5.3 – ISE ADaM had 169295 errors in the ADLB (Analysis Dataset Laboratory Tests) domain and 14141 errors in the ADSL (Analysis Dataset Subject Level) domain – those of concern include:
 - i. 154825 errors in ADLB domain. The errors were reported as “CRITy is populated as Seroconversion and CRITyFL is not populated.” The rule

- states “When CRITy (Analysis Criterion) is populated; its corresponding Analysis Criterion Y Flag must be populated.” CRITy and CRITyFL are set to null for rows within the parameter where the criterion is not met or is unevaluable. Please explain whether null in CRITyFL is unevaluable or not, and correct as needed.
- ii. 14139 errors in ADSL domain Race variable. The errors were reported as “Null value in variable marked as Required.” The validation rule SD1008 states that “Required variables (where Core attribute is 'Req') cannot be null for any record.” The Race variable is a required variable and cannot be left blank (ADaM implementation guide v 1.1). Please explain why the values are null and correct as needed.
- d. In Section 5.3.5.3 – ISS (Integrated Summary of Safety) SDTM had 127601 errors in the 10 SDTM datasets - those of concern include:
- i. 156 errors in the AE (Adverse Events) domain; the errors were reported as “Begin day must be less than or equal to end day.” The validation rule SD0012 states that “Identifies records that violate the condition (Study Day of Start of Observation less than or equal to Study Day of End of Observation), limited to records where [Study Day of Start of Observation is not null and Study Day of End of Observation is not null].” For example, in record 6806 of raw data, AESTDTC was populated as 1997-10-19 but AEENDTC was populated as 1994-10-25. This implied that adverse event (Benign Prostatic Hyperplasia) of the patient began in 1997 and resolved in 1994 which is not possible. Please correct the errors.
 - ii. 102647 errors in CE (clinical events) domain. The errors were reported as “Duplicate value for CESEQ variable.” The rule of SD0005 states that “the value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within the Unique Subject Identifier (USUBJID) or Pool Identifier (POOLID) variables value when they are present in the domain.” For example, in record 178278 of raw data, CESEQ was populated as 64 for USUBJID V7P18-01007. However, in record 178381 of raw data, CESEQ was populated as 64 for USUBJID V7P18-01008. Please explain and correct the errors.
 - iii. 1259 errors in DM (Demographics) domain: the errors were reported as “Duplicate USUBJID.” The validation rule SD0083 states that “The value of Unique Subject Identifier (USUBJID) variable must be unique for each subject across all trials in the submission.” Please explain and correct the errors.
 - iv. 1259 errors found in EX (Exposure) domain reported as “Duplicate value for EXSEQ variable.” The rule of SD0005 states that “the value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within of Unique Subject Identifier (USUBJID) or Pool Identifier (POOLID) variables value when they are present in the domain.” For example, in record 1971 of raw data, EXSEQ was populated as 1 for USUBJID V7P18-01064. However, in record 1972 of raw data, EXSEQ

was also populated as 1 for USUBJID V7P18-01065. Please explain and correct the errors.

- v. 1 error found in IE (Inclusion and Exclusion) domain reported as “Inconsistent value for IETEST within IETESTCD.” The rule of SD0040 states that “All values of Name of Measurement, Test or Examination (--TEST) should be the same for a given value of Short Name of Measurement, Test or Examination (--TESTCD).” For example, in record 17 of raw data, IETESTCD was populated as EXCL06 and IETEST was populated as “Infections requiring systemic antibiotic or antiviral therapy within the past 7 days. However chronic antibiotic therapy for urinary tract prophylaxis is acceptable.” As compared with record 2 in raw data, IETESTCD was populated as EXCL06 and IETEST was populated as “Individuals with infections requiring systemic antibiotic or antiviral treatment within seven days prior to the study vaccine administration.” Thus IETESTCD are the same for above two records but IETEST are different. Please correct the error.
- vi. 853 errors found in MH (Medical History) domain reported as “Duplicate value for EXSEQ variable.” The rule of SD0005 states that “the value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within the Unique Subject Identifier (USUBJID) or Pool Identifier (POOLID) variables value when they are present in the domain.” For example, in record 8147 of raw data, EXSEQ was populated as 1 for USUBJID V7P25-01483. However, in record 8149 of raw data, EXSEQ was also populated as 1 for USUBJID V7P25-01484. Please correct the errors.
- vii. 3 errors found in RELREC domain reported as “Referenced record not found.” The rule of SD0077 states that “Identifies Related Records domain reference to a record that doesn't exist in the target domain.” For example, in record 7994 of raw data RELREC domain, RDOMAIN MH MHSPID 4 refers to a target record of CMSPID 0100503 that does not exist in CM domain. IDVARVAL values for CMSPID were not populated in a correct way. Please correct the errors. Please look at SDTMIG v3.1.3. (page 258 example 2) as a reference.
- viii. 3657 errors found in SE (Subject Elements) domain reported as “Non-unique value for ELEMENT within ETCD.” The rule of SD1027 said that “Description of Element (ELEMENT) must have a unique value for a given value of Element Code (ETCD) within the domain.” For example, in record 3211 of SE domain, ETCD was populated as FLUAD and ELEMENT was populated as FLUAD0003 and the EPOCH was populated as Second treatment EPOCH. However, in record 3210 of SE domain, ETCD was populated as FLUAD and ELEMENT was populated as FLUAD0003, but the EPOCH was populated as First treatment EPOCH. Records 3210 and 3211 are different in EPOCH, but ELEMENT was not unique to tell the difference. Please correct the errors.

- e. In Section 5.3.5.3 – ISS ADaM had 7 errors in ADAE (Analysis Datasets Adverse Events) domain, 16622 errors in ADCE 2 (Analysis Datasets Clinical Events 2) domain, 4 errors in ADCM (Analysis Datasets Concomitant Medications) domain, 4 errors in ADEX (Analysis Datasets Exposure) domain, 4 errors in ADMH (Analysis Datasets Medical History) domain and 14141 in ADSL domain. Those of concern include:
- i. 3 errors in ADAE domain were reported as “STDY must be less than or equal to ENDY.” The validation rule SD0099 states that “Any variable ending in SDY (Start day) must have a value less than or equal to its corresponding EDY (end day) value.” In raw data, the variable AENDY in records 6409, 7400 and 7401 are negative value. That means AENDY is less value than AESDY. Please explain this error and correct as needed.
 - ii. 16622 errors in ADCE2 domain. The errors were reported as “Inconsistent value for AVALC.” The rule states “For a given value of Analysis Value Numeric (AVAL), all values of Analysis Value Character (AVALC) should be the same for a given PARAMCD.” In the raw data record 1-102 AVALC is blank, but record 102 to 39043 are filled with ‘any or NO.’ The PARAMCD is the same from record 1 to 39043. Please explain why some AVALC are blank while others are filled with ‘any or NO’ with the same PARAMCD. Please correct as needed.
 - iii. 14141 errors in ADSL domain Race variable. The errors were reported as “Null value in variable marked as required.” The rule states that “required variables (where Core attribute is 'Req') cannot be null for any record.” Please explain and correct as needed.
 - iv. 4 errors were found in ADCM domain. The errors were reported as “Neither AVAL nor AVALC are present in dataset.” The AD1005 rule states “At least one analysis value (numeric or character) is not present in BDS.” ADCM belongs to BDS. AVAL is required if AVALC is not present since either AVAL or AVALC must be present. Please correct the errors.
 - v. 3 errors were found in ADEX domain. One error was reported as “Neither AVAL nor AVALC are present in dataset.” The AD1005 rule states “At least one analysis value (numeric or character) is not present in BDS.” ADCM belongs to BDS. Please correct this error. Two errors were reported as “Required PARAM is not present within dataset. Required PARAMCD is not present within dataset” and “Required PARAMCD is not present within dataset.” The rule states in AD1001 that Variables described in ADaM as Required must be included in the dataset. Please add PARAM and PARAMCD into the ADEX domain.
 - vi. 3 errors were found in ADMH domain. One error was reported as “Neither AVAL nor AVALC are present in dataset.” The AD1005 rule states “At least one analysis value (numeric or character) is not present in BDS.” ADMH belongs to BDS. Please correct this error. Another error was reported as “Required PARAM is not present within dataset.” PARAM is a required variable in BDS and is used to describe the analysis

parameter. For example, in record 19 of raw data, the value of MHTERM is Arterial Hypertension. PARAM should be populated as “Arterial Blood Pressure (mmHg).” However, this information was missing. Please correct the error if possible. One error was reported as “Required PARAMCD is not present within dataset.” The AD1001 rule states “Variables described in ADaM as required must be included in the dataset.” PARAMCD is the short name of the analysis parameter in PARAM. Please correct the error if possible.

2. In our validation of CDISC, we noted that the CDISC code list was not consistently used. For example, there were 282,715 major warnings in clinical events because the term “left deltoid” used for the injection site was used instead of “left arm.” In addition, SOC controlled terminology (MedDRA standard hierarchy) was not always used. For example, 32,857 major warnings were in medical history because “Circulatory System” used in MHBODSYS is not an SOC controlled term. While no action is required for this BLA, we request that in the future these discrepancies be sought, and corrected if present, prior to BLA submission.

Clinical:

3. Review of the SDTM database in sections 5.3.5.1 “Data tabulation dataset legacy” and 5.3.5.3-ISS “data tabulation dataset legacy” reveals significant inconsistency in how different AE terms were categorized by system organ class (SOC). For example, hypertensive episodes could be found under “Investigations” or “Vascular Disorders” or “Cardiac Disorders” or “Nervous System Disorders.” Please revise this database such that all of the same type of event is categorized under one SOC.
4. Regarding your response on February 12, 2015 (amendment 3) to our question about the HAI assay test and titer calculation by (b) (4), we have noted that the volume of virus (b) (4). Please correct accordingly the HAI titer of all subjects impacted by this error and provide the revised titers to the BLA no later than March 23, 2015.
5. With regard to the above modifications noted in clinical questions #3 and #4, we anticipate correction of these data sets will impact many of the figures, tables, and text in the clinical study report. Please submit a new updated (both clean and tracked changes) version of the clinical study report with tables, text, and figures reflecting these modifications to the BLA no later than May 4, 2015. Please include in this updated version the changes previously submitted in section “5.3.5.1 V70_27 add” and section “5.3.5.1 V70_27-Post-hoc” so that all current data descriptions and analyses can be obtained in one complete CSR document.

CMC:

6. In 3.2.P.3.5 Attachment 2, Table 9, 10, 11 you provide the results of stability testing of sterile MF59C.1 (b) (4) adjuvant batches (b) (4) manufactured in (b) (4). In Table 8 of the same attachment, you provide the plan for stability studies of the sterile MF59C.1 (b) (4) adjuvant that covers (b) (4). In support of the stability of sterile (b) (4) adjuvant, please provide a complete stability report for batches (b) (4) manufactured in (b) (4) including sterility testing at (b) (4).
7. Since you intend to use sterile MF59C.1 (b) (4) adjuvant stored no longer than (b) (4) for the formulation of the FLUAD vaccine, please revise your stability protocol for the sterile MF59C.1 (b) (4) adjuvant and include sterility testing at the (b) (4) time point.
8. Per your Drug Product specification table 3.2.P.5.1-1, some release tests are conducted at Final Bulk, some at Final Filled Vaccine, and some at both stages. For influenza products, concurrent testing by the FDA is usually conducted at the Final Bulk stage to facilitate expeditious release of product. CBER requests that you conduct and report results of all release tests at the Final Bulk stage, regardless of whether the tests are performed for the Final Bulk and/or the Final Filled Vaccine. This will facilitate accelerated CBER lot release of product consistent with other similar influenza vaccine products. Please respond.
9. We have following questions regarding the Haemagglutinin Content Determination by Single Radial Immunodiffusion (SRID) assay:
 - a. **Section 3.2.P.5.2 Analytical Procedures-Hemagglutinin (b) (4) Content SRID:** In reference to testing of formulated drug product on page 2 you have mentioned that the “same basic methodology is applied to (b) (4) samples as to (b) (4) Final Filled Product with slight differences. DP is tested using (b) (4) for Filled samples.”

In the SRID assay, (b) (4)

(b) (4) Since the samples of (b) (4) filled product contain the MF59C.1 adjuvant, please clarify whether any modifications to the SRID assay are necessary for HA content determination.
 - b. Please provide a copy of the current SOP for the determination of Hemagglutinin (b) (4) Content by SRID in the FLUAD vaccine covering testing of (b) (4) final container DP.
 - c. **In reference to SRID Validation:** For the SRID assay the reference standard is prepared in an (b) (4) while the final formulated FLUAD vaccine contains adjuvants. No data has been provided in the SRID validation reports that describes the effect or the lack of effect of the presence of adjuvant upon the

performance or accuracy of the SRID assay for measurement of HA content. Please clarify.

- d. **Section 3.2.P.5.3:** An “Interim Analytical Method Transfer Report” (attachment 42 LVP transfer report) describing the transfer of method for determination of hemagglutinin content (b) (4) from (b) (4) has been included. For method transfer, (b) (4) batch of a (b) (4) final product was used. In reference to this report please clarify the following:
- a) Why was a (b) (4) trivalent) product used in this evaluation?
 - b) The cross reactivity of the B-strain antibodies may impact the measurement of HA content for B-strains in a (b) (4) SRID assay. Please clarify the approach used to measure the amount of HA for B-strains in the (b) (4) sample.
 - c) On page 9 of the report you have mentioned that “Reagents were all qualified in (b) (4), reagent usage details used as detailed in (b) (4) document 257612.” Please provide a copy of document 257612.
10. Please confirm if the manufacturing facility in (b) (4) will be used in the production of monovalent antigens and microbiological testing of the drug substance and drug product.
11. The validation for the Sterility Test (Report CST 07.001 VR 102 Rev. 8) was performed in the (b) (4) facility, but the sterility test on the drug product will be performed in the (b) (4) facility; therefore CBER requests that the sterility test validation in (b) (4) include showing that the test method is suitable for known environmental isolates from the (b) (4) facility, if applicable.
12. We note that the information for the (b) (4) analytical procedures is only provided under the (b) (4) MPH section. Please clarify if these analytical procedures are also performed at the (b) (4) facility

Please submit your response in a timely manner or submit a partial response, so we may continue the review of your application. We recommend that you restate each item and follow it with your response. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference. If we determine that your response to this information request constitutes a major amendment which will extend the review period an additional three months, we will notify you in writing.

If you have any questions, please contact the Regulatory Project Manager, Theodore Garnett, Ph.D., at (301) 796-2640.