

RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125510/0 Office: OVRR

Product:
Influenza Vaccine, Adjuvanted

Applicant:
Novartis Vaccines and Diagnostics, Inc.

Telecon Date/Time: 20-July-2015 1:23 PM Initiated by FDA? N/A

Telephone Number: N/A – E-mail communication

Communication Category(ies):
1. Other, Advice

Author: Theodore Garnett

Telecon Summary:
CBER recommendation and Novartis response regarding the lots of trivalent bulk to be submitted for testing

FDA Participants: Brenda Baldwin and Theodore Garnett

Non-FDA Participants: Mayuresh Gadre

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

From: GADRE, MAYURESH [mailto:mayuresh.gadre@novartis.com]

Sent: Monday, July 20, 2015 1:23 PM

To: Baldwin, Brenda

Cc: Garnett, Theodore

Subject: RE: STN 125510/0 (FLUAD 65): Request for information

Hi Brenda,

Please see below for Novartis' response to your email on June 24, 2015.

CBER Comment:

The 3 lots of trivalent bulk formulation must be manufactured using the validated production processes proposed in the BLA.

Novartis Response:

Novartis acknowledges that the Agency has stated that material must be manufactured using the validated production processes proposed in the BLA. Monovalent bulk antigens and MF-59 material will be used from processes that have been validated, are at the commercial scale and are representative of what will be used when Flud is launched in the US.

Novartis will formulate 3 x (b) (4) Flud batches in the US licensed (b) (4) at the next available timeslot currently identified for the week of (b) (4). Novartis is working to further accelerate the manufacturing schedule to ensure deliver of formulated trivalent bulk samples to CBER by the end of August. The foreseeable timeframe for the receipt of samples at CBER is between August 28, 2015 and September 8, 2015. We will communicate the confirmed sample delivery date by August 15, 2015.

CBER Comment:

The 3 lots that you formulate must meet US specifications. You do not need to target different potencies with each formulation.

Novartis Response:

The 3 lots manufactured will be formulated to meet US specification. Different potencies will not be targeted with each formulation. It should be noted that US SRID test results obtained on (b) (4) material intended for use in formulation indicates that the maximum formulation potency strength will be approximately (b) (4).

CBER Comment:

You will need to submit batch protocols with test results for all US specifications which have been conducted at a time close to submission of the lots to CBER.

Novartis Response:

An updated lot release protocol has been provided in the company's response to Information Request dated 15 May 2015 (submitted on July 17, 2015 in Sequence 0016). The lot release protocol will be completed for each lot of formulated bulk generated. Completed lot release protocols will be sent within 2-3 weeks from receipt of lots by CBER.

CBER Comment:

We will need to receive these trivalent bulk lots by no later than late August in order to complete our testing.

Novartis Response:

The foreseeable timeframe for the receipt of samples at CBER is between August 28, 2015 and September 8, 2015. We will communicate the confirmed sample delivery date by August 15, 2015.

Please let me know if you have any questions.

Best Regards,
Mayuresh

Mayuresh Gadre

Senior Regulatory Affairs Specialist,
Regulatory Affairs North America
Novartis Vaccines and Diagnostics, Inc.
Phone: 617-871-8384
Email: mayuresh.gadre@novartis.com

From: Baldwin, Brenda [<mailto:Brenda.Baldwin@fda.hhs.gov>]
Sent: Wednesday, June 24, 2015 3:42 PM
To: GADRE, MAYURESH
Cc: Garnett, Theodore
Subject: RE: STN 125510/0 (FLUAD 65): Request for information

Hi Mayuresh,

We agree with your proposal with the following qualifications:

- The 3 lots of trivalent bulk formulation must be manufactured using the validated production processes proposed in the BLA, and
- The 3 lots that you formulate must meet US specifications. You do not need to target different potencies with each formulation, and
- You will need to submit batch protocols with test results for all US specifications which have been conducted at a time close to submission of the lots to CBER.
- We will need to receive these trivalent bulk lots by no later than late August in order to complete our testing.

Regards,
Brenda

From: GADRE, MAYURESH [<mailto:mayuresh.gadre@novartis.com>]
Sent: Monday, June 22, 2015 2:01 PM
To: Baldwin, Brenda
Cc: Garnett, Theodore
Subject: RE: STN 125510/0 (FLUAD 65): Request for information

Hi Brenda,

Novartis' response for the number of monovalent bulks available for formulation is provided below:

"Novartis currently has (b) (4) from the 2014/15 NH campaign manufactured in (b) (4) under the validated Agriflu drug substance production process. Novartis has (b) (4) of each strain available. This material will be used to perform (b) (4) formulations within the Manufacturing Sciences and Technology group of Novartis. (b) (4) formulation is performed within a (b) (4). The (b) (4) process is representative of the (b) (4) production process presented in the BLA and will be tested against the proposed US test specifications.

Three separate trivalent bulks will be formulated, however these trivalent bulks will use the (b) (4) monovalent bulks to perform the (b) (4) formulations. Novartis proposes

to formulate (b) (4) different potency concentrations. Approximately (b) (4) of trivalent bulk will be made available for CBER's use.

As discussed previously, analytical testing will be required pre/ post formulation which, based upon the agreed panel of tests required, will take approximately six weeks to complete. Based on internal activities related to the 2015/16 campaign the aim will be to provide material by the end of Q3 2015."

Best Regards,
Mayuresh

Mayuresh Gadre
Senior Regulatory Affairs Specialist,
Regulatory Affairs North America
Novartis Vaccines and Diagnostics, Inc.
Phone: 617-871-8384
Email: mayuresh.gadre@novartis.com

From: Baldwin, Brenda [<mailto:Brenda.Baldwin@fda.hhs.gov>]
Sent: Thursday, June 18, 2015 2:04 PM
To: GADRE, MAYURESH
Cc: Garnett, Theodore
Subject: RE: STN 125510/0 (FLUAD 65): Request for information

Mayuresh,

We agree that the use of the Drug substance corresponding to the same strains used in the 2014/15 NH campaign can be used to perform (b) (4) formulations within the Manufacturing Sciences and Technology group within Novartis, as long as they are performed using the validated production processes proposed in this BLA. (b) (4) formulations will need to meet US test specifications; however, you can test for potency with reagents from the EU as long as you provide those same reagents to us for analysis of the formulated trivalent bulks. (b) (4) separate trivalent bulks can be formulated; however the use of the (b) (4) monovalent bulks to perform the (b) (4) formulations would not be desirable. Please indicate if you have more than (b) (4) monovalent bulk of each.

The formulated trivalent bulk will be used for both assay development and in support testing. You can assume that all tests noted in your BLA for the formulated trivalent bulk will be performed to analyze your sample formulations.

Please provide your response to the number of monovalent bulks available for formulation to me no later than noon Monday June 22, 2015.

Regards,
Brenda

From: GADRE, MAYURESH [<mailto:mayuresh.gadre@novartis.com>]
Sent: Monday, June 08, 2015 4:16 PM
To: Baldwin, Brenda

Cc: Garnett, Theodore

Subject: RE: STN 125510/0 (FLUAD 65): Request for information

Dear Brenda,

The company proposal for providing additional samples for testing in support of the BLA 125510 is outlined below:

Following internal discussions, there is currently no scheduled Fluad manufacture to US specification for the forthcoming 2015/16 NH campaign.

Novartis also confirms that although the formulation process for the EU and US is the same, the potency of the monovalent bulks are tested based on the market or territory to be supplied (i.e. EU reagents/assay /specification for EU and ROW countries or US reagents/assay/ specification for product marketed within the US), with the results used in the blend calculation.

Differences in the reagents / assays /specification may result in an OOS for a particular formulation. For example, an EU formulation may result in a result falling below specification when tested using US reagent / assay / specification combination.

With regard to the request for additional Fluad material, Novartis is working toward resolving the following issues to provide material to FDA as soon as possible;

- 1) Difference in reagents
- 2) No drug product material left over from the 2013/14 or 2014/15 campaigns
- 3) No Fluad stock were made for 2015 SH campaigns

Therefore, with regards to the request for additional Fluad material to use within development studies at CBER, the company would like to propose the following approach if it is acceptable and meets the required standard for CBERs intended use of the material.

Drug substance corresponding to the same strains used in the 2014/15 NH campaign is available. This material can be used to perform (b) (4) formulations within the Manufacturing Sciences and Technology group within Novartis. (b) (4) formulation can be performed within a (b) (4), following the same formulation calculation and material to result in a formulated DS representative of the (b) (4) manufacturing process.

(b) (4) formulations can be performed to US test specification (i.e. (b) (4) can be tested using US reagents / SRID assay and (b) (4) according). (b) (4) separate bulks can be formulated and if required to (b) (4) different potency concentrations, however the use of the (b) (4) may be required. Release analysis of the bulks can be performed and provided for the (b) (4) lots manufactured.

With regards to the timeline for supply of such material, analytical testing will be required pre/ post formulation which based upon the agreed panel of tests required may result in a total time line of up to six weeks to complete. As you appreciate, confirmed analytical slots will need to be scheduled prior to confirmation of the exact time line of provision of

material as we are currently within the 2015/16 commercial manufacturing and release campaign. The aim will be to provide material by the end of Q3 2015.

In order to establish if this is an acceptable approach, the company would like to request clarification of the use of the material, e.g. is this for the purpose of assay development, evaluation. If so, the company would like to know specifically which assays the material will be used for e.g. sterility testing as this will impact upon the panel of testing to be performed on the formulated material. Any additional information you can provide will aid in the preparation of material.

Please let me know if you have any questions.

Best Regards,
Mayuresh

Mayuresh Gadre
Senior Regulatory Affairs Specialist,
Regulatory Affairs North America
Novartis Vaccines and Diagnostics, Inc.
Phone: 617-871-8384
Email: mayuresh.gadre@novartis.com

From: Baldwin, Brenda [<mailto:Brenda.Baldwin@fda.hhs.gov>]
Sent: Friday, June 05, 2015 2:44 PM
To: GADRE, MAYURESH
Cc: Garnett, Theodore
Subject: FW: STN 125510/0 (FLUAD 65): Request for information

Hi Mayuresh,

As discussed last Friday, May 29th, we do understand your rationale for not being able to provide launch lots until next year; however, we have insufficient material to complete our testing for this BLA. As requested, we will need samples from 3 lots of bulk formulated vaccine (Final Bulk) representing the manufacturing process described in the BLA. These samples may be from the 2013-14, 2014-15 or 2015-16 season (provided that the strain information is available). If the samples provided have expired, then you will need to provide current test results so that we are able to confirm your data. You had agreed that you would provide to me your proposal on the lots that could be submitted for testing. Could you please provide this information to me no later than June 8th?

In regards to submitting a strain change supplement in the future, if this BLA gets approved, you will need to submit the supplement to STN 125510.

Regards,
Brenda

From: GADRE, MAYURESH [<mailto:mayuresh.gadre@novartis.com>]
Sent: Friday, May 22, 2015 2:48 PM

To: Garnett, Theodore

Subject: RE: STN 125510/0 (FLUAD 65): Request for information

Dear Ted,

I had a question regarding the Information Request received on May 15, 2015.

1. For CBER comment 13; ***13. Please provide information on the 2015-2016 strain change to support the adjuvanted trivalent final bulk samples of FLUAD that represent lots for release of which you will be providing in the near future***

Reference is made to the information request sent by CBER on 23rd Jan 2015 for Flud samples for method Development. In response (Feb 2015), Novartis indicated that it would provide the agency material for BLA testing from the 2015/16 NH influenza campaign and that the availability of that material would be "made known following the following the 2015/16 strain announcement and upon availability of US specific reagents."

Novartis would like to clarify that the 2016-2017 Northern Hemisphere season will be the first commercial campaign in the US market.

Therefore, can the Agency clarify whether a supply of monovalent and filled drug product lots relating to strains from the 2016/17 season alone will suffice the requirements for BLA testing. Can the Agency also clarify whether or not information on the 2015/16 strain change is still required.

Furthermore, Novartis proposes to provide the associated NH 2016/17 strain change in the annual update to the Agriflu BLA (BLA# 125297) in (b) (4). Does the Agency agree with this approach?

I also wanted to provide you with an update on the MF59 sample requested. The sample was shipped to CBER on May 21, 2015 and has been delivered on May 22, 2015 (at 10:08 AM, signed by HOLMES). The tracking number is (b) (4) for your reference.

Best Regards,
Mayuresh

Mayuresh Gadre
Senior Regulatory Affairs Specialist,
Regulatory Affairs North America
Novartis Vaccines and Diagnostics, Inc.
Phone: 617-871-8384
Email: mayuresh.gadre@novartis.com

From: Garnett, Theodore [<mailto:Theodore.Garnett@fda.hhs.gov>]

Sent: Friday, May 15, 2015 4:31 PM

To: GADRE, MAYURESH

Subject: STN 125510/0 (FLUAD 65): Request for information

Importance: High

Dear Mayuresh,

Please find attached a new request for information from CBER. Feel free to contact me if you have any questions or concerns.

Best regards,

Ted

Theodore Garnett, Ph.D.

LCDR, U.S. Public Health Service

Microbiologist (Regulatory)

U.S. Food and Drug Administration

CBER|OVRP|DVRPA|CMC3

10903 New Hampshire Avenue

Silver Spring, MD 20993

Office: 301-796-2640

Cell: (b) (6)

U.S. Public Health Service Rapid Deployment Force PHS-2 ("*Second to None*") Admin/Finance
Section, Home Support Branch Director

"THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone."