

Record of Telephone Conversation, September 13, 2012 - Flucelvax

Submission Type: BLA Submission ID: 125408/0 Office: OVRR
Product:
Influenza Virus Vaccine
Applicant:
Novartis Vaccines and Diagnostics, Inc.
Telecon Date/Time: 13-Sep-2012 12:00 AM Initiated by FDA? Yes
Telephone Number:
Communication Category(ies):
1. Advice
2. Information Request

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Telecon Summary:

Absence of extraneous virus, SRID testing reagents

FDA Participants: Rajesh Gupta

Non-FDA Participants: Matthew Gollwitzer, Umang Shah

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

Regarding CBER Query # 2 from e-mail sent to NVD on 9-7-12: *Please clarify at which stage the "Absence of extraneous viruses" testing will be performed----- (b)(4)----- . If these tests will be performed after the -----(b)(4)-----, please comment on whether these processes would affect the test results.*

Dr. Gupta's Comments: The testing should be performed -----(b)(4)----- to prevent inactivation or filtering out of the adventitious viruses prior to detection

NVD Comments: NVD acknowledged Dr. Gupta's concerns; however, NVD was concerned with the lower limit of detection -----(b)(4)----- . Novartis committed to re-evaluating the limit of detection of adventitious agents at the ---(b)(4)---- -- step.

Regarding CBER Query # 4 from e-mail sent to NVD on 9-7-12: *Because a cell-based reference antigen for B/Wisconsin is available from NIBSC, CBER recommends using this reference for SRID testing. Please comment.*

Dr. Gupta's Comments: Dr. Gupta emphasized employing homologous antigens for SRID testing. CBER prefers use of homologous strain reagents, unless there is an emergency situation, like a pandemic. Egg based reagents can be used for a cell culture manufactured product, when the strain is same and it has been demonstrated

that the egg based reagents are suitable for cell culture based product. In this situation, there are two variables, heterologous strain and vaccine and reference made in different host systems. Dr. Gupta inquired whether for Europe, where Optaflu has been approved, which reagents were employed

NVD Comments: NVD acknowledged Dr. Gupta's concerns and stated that NIBSC reagents could have been employed. Based on e-mail communication between CBER and NVD in April, Holly Springs assumed that reference antigen B/Hubei-Wujiagang/158/2009, BX-39 and antiserum B/Hubei-Wujiagang/158/2009 provided by CBER would be available and suitable for the manufacturing campaigns to determine the HA yield in the monobulk. They noted that if the SRID method did not demonstrate suitability for use with these reagents further evaluation would then need to occur using either the B/Texas reagents or if available the cell culture based B/Wisconsin reagents. NVD will submit the verification and qualification reports demonstrating suitability of the egg based reagents.

Post Teleconference Update from NVD: NVD has employed cell based NIBSC reagents for release in Europe. The NIBSC reagents became available in mid June in Europe post e-mail communication with CBER in April. NVD shipped whole inactivated B/Wisconsin virus to CBER in April for the preparation of cell derived antigen standard and also to allow evaluation of the BX39 reagent set with cell derived material. Based on the earlier discussions and guidance back in Nov 2011, Feb 2012 and also based on April-May 2012 communication with CBER NVD planned all activities based on the use of egg based reagent qualification. NVD progressed to test mono bulks using these egg-based reagents and generated values for the trivalent formulation. NVD is seeking further path forward for 2012 flu season. Considering this situation and to ensure complete understanding of the scenarios, Novartis is looking to put together a position paper to address timing, availability and utilization of CBER and NIBSC egg based and/or cell based homologous and/or heterologous reagents to ensure future alignment and agreement

Regarding CBER Query # 5 and # 6 (combined) from e-mail sent to NVD on 9-7-12:

CBER Query # 5: *The information provided by Novartis via e-mail on September 5, 2012 for CBER comment 11a did not include the residual infectious virus validation documents with virus lots and titers as requested in the August 24, 2012 telecon between CBER and Novartis. Please provide this information.*

CBER Query # 6: *In the information provided by Novartis via e-mail on September 5, 2012 for CBER comment 11b, Novartis did not discuss the 2 options agreed upon by CBER and Novartis in an August 24, 2012 telecon. Please comment on the options described below.*

Option 1: *If Novartis is unable to provide validation data demonstrating that the test for residual infectious virus performed in ---(b)(4)--- is at least as sensitive as the test performed in ----(b)(4)-----, Novartis should test the first 3 ----(b)(4)----- lots from each annual influenza season for residual infectious virus in both the -----(b)(4)----- . All 3 lots for all seasonal strains must pass the test in both*

substrates. Subsequent lots manufactured during the season can be tested by the --(b)(4)---- method only.

Option 2: Alternatively, if Novartis can provide validation data demonstrating that the sensitivity of the residual infectious virus test performed in ---(b)(4)----- is at least as great as the test performed in ----(b)(4)-----, then Novartis may release -----(b)(4)----- by the test performed in ---(b)(4)---- only. A possible experiment suggested by CBER to validate the sensitivity of the assay which should be demonstrated for at least 3 strains representing H1N1, H3N2 and B types was as follows: ----(b)(4)----- lots (at least 3 lots for each strain) spiked with serial dilutions of the same strain of MDCK cell grown influenza virus of known concentration ---(b)(4)---- units) should show at least similar or higher sensitivity in detecting spiked virus by the --(b)(4)---- test as compared to the -----(b)(4)----- test. As per the theoretical explanation provided by Novartis during the August 24, 2012 telecon that the sensitivity of ---(b)(4)--- is significantly higher than the ----(b)(4)-----, CBER suggested that Novartis could perform the test at one spike level of ----(b)(4)----- and show that such a spike cannot be detected by (b)(4), but could be readily detected by (b)(4)

Dr. Gupta's comments: Dr. Gupta indicated he was aware of the information already provided in the BLA. It seemed that there was no new information available and information already provided is not sufficient. A path forward would be to agree on Option 1 and/or Option 2. Dr. Gupta acknowledged NVD could use ----(b)(4)----- assay for -----(b)(4)----- for RIV concurrently with the ---(b)(4)---- assay.

NVD Comments: NVD acknowledged Dr. Gupta's concerns and will proceed with Option 1 while pursuing Option 2 concurrently to phase out additional testing if equivalency/superiority of ---(b)(4)----- assay established. NVD stated that for the 2012 flu season the ---(b)(4)----- will be tested immediately using the validated assay to test -----(b)(4)----- . The ----(b)(4)---- assay results are expected by Sep 26 with a report soon thereafter. For 2013 flu season NVD will test first three lots of ----(b)(4)---- employing ----(b)(4)----- assays until Option 2 established sensitivity of (b)(4) assay.