

Teleconference, November 20, 2014 - BEXSERO

Application type and number: BLA 125546/0

Product name: Bexsero, Meningococcal Group B Vaccine

Proposed Indication: Active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age

Applicant: Novartis Vaccines and Diagnostics, Inc.

Meeting date & time: November 20, 2014, 12:00 PM

Subject: Teleconference requested by Novartis to discuss and clarify CBER's November 12, 2014, (b)(4) and Potency IR comments

CBER Attendees:

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|------------------|---------------------------------|
| Margaret Bash | Review Committee Chair |
| Edward Wolfgang | Lead Regulatory Project Manager |
| Kirk Prutzman | Regulatory Project Manager |
| Ramachandra Naik | Regulatory Project Manager |
| Freyja Lynn | Assay Reviewer |
| Tsai-Lien Lin | Assay Reviewer |

Novartis Attendees:

| | |
|-----------------|-----------------------|
| Rino Rappuoli | Head of Development |
| James Wassil | Product Lead |
| Manish Vyas | Head Regulatory |
| Patricia Stoehr | Regulatory |
| Joe Crowell | Project Management |
| Davide Serruto | Technical Development |
| Alex Pysik | Statistics |
| Michael Collins | Project Management |

Discussion Summary:

CBER's November 12, 2014, IR comments are below. Discussions of each comment that occurred during the teleconference are in italics.

Please respond to the following comments by either providing the data requested or providing reasonable timelines for conduct of the work requested and submission of the data.

1. The tests for the potency of the --(b)(4)-- antigens appear to be more variable than those for the other antigens. We believe this may be due in part to the (b)(4)-- conditions being used to assess the antibodies in the (b)(4)- serum. Please further optimize the assay used to quantitate the antibodies to (b)(4)--.

Discussion: When asked to provide more detailed information concerning this comment, CBER explained that the data submitted on (b)(4) lots showed much more variability around the potency of (b)(4) relative to the other recombinant proteins.(b)(4) CBER suggested that Novartis examine the dilutions used to

generate the assay reference standard curve as the data suggest it may be too shallow. CBER added that only (b)(4) sample was used to show precision so the precision and accuracy are unknown at the extremes of the assay. Novartis acknowledged the variability issue and agreed to optimize the assay.

2. Please re-examine the dose response data in the immunogenicity test and provide additional data that verify that the optimum doses are being used to generate the dose response curve. Please provide data that verify that the dose levels and number of doses used are adequate to minimize the overall variability of the assay. *Discussion: Novartis requested clarification on CBER's expectations and indicated that more data were available than had been submitted to CBER. CBER explained that the data submitted to date showed a shallow response curve without much depth for some of the antigens. Doses that are either too close together or do not span the optimum range would likely increase variability due to the uncertainty around the slope of the dose response curve. CBER suggested that Novartis look at the data to make sure the optimum doses are being used for the range. CBER indicated that the choice of strains and the number of doses used is probably appropriate.*
3. Please re-evaluate the system suitability criteria for both the (b)(4)- and potency estimation to further verify that the criteria are rejecting assays that are performing outside expected performance criteria.
 - a. For the (b)(4)--, please indicate the statistical basis for the system suitability criteria and the likelihood of rejecting assays due to chance alone.
 - b. The system suitability criteria for the (b)(4) potency test were based on simulated data. Please update the criteria using data from the assays run to date. Please indicate the likelihood of rejecting assay due to chance alone.*Discussion: Novartis agreed with this request.*
4. Please revalidate the (b)(4)-- in the laboratory in which the assays are performed for product release. Validation studies should mimic routine use. Accuracy and precision should be demonstrated using incurred and mock samples across the working range of the assay. The lower limit of quantitation (LLOQ) should be based on sample accuracy and precision at the reported LLOQ. *Discussion: Novartis requested ongoing input from CBER on the revalidation of the test. CBER suggested that Novartis and CBER could collaborate either via a Technical Working Group or through IND submissions and review. CBER and Novartis agreed to discuss this further once a timeline for the CBER requests had been established.*
5. We find the specification for the Upper Confidence Limit to be inadequate as it does not provide relevant information regarding the potency of the product. As communicated to you previously, Upper Confidence Limit is not a proper way of ensuring non-inferiority of a test lot, especially given the large variability of your potency assay. Although you showed in your responses submitted to Amendment 4 that with the additional criterion of the point estimate of RP being (b)(4), the chance of passing a subpotent lot is extremely low when the relative potencies of all four components are only (b)(4), the probability of falsely accepting a lot with RP slightly below (b)(4) or with low RP for only one or two of the four components can be high. Please discuss the use of a criterion based on the confidence limits to eliminate

assay data from tests that are not precise enough to provide confidence in the point estimate of potency.

Discussion: Novartis agreed with this request.

6. Please propose drug product specifications based on the historical performance of the (b)(4) lots released since the introduction of the latest potency test. Please provide a comparison of the proposed specifications to the potency of lots shown to be immunogenic in clinical studies to demonstrate that the product as currently tested is similar to those clinical lots.

Discussion: Novartis indicated that they could do this but would likely select a subset of lots and include rejected lots as well to ensure the distribution was not overly narrow. CBER indicated that Novartis will need to address the randomness of the data and to pick more appropriate data (avoiding bias) while making a comparison of the proposed specifications to the potency of lots. Novartis agreed to submit a proposal for review before doing the analysis.

7. The ability of the potency test to detect degraded vaccine was determined by -----(b)(4)----- . If the current potency specifications are applied to the results, the data are inconsistent with regard to the ability of the assay to detect changes in the component antigens. The only antigen consistently affected by -----(b)(4)----- . Please provide additional data to demonstrate that the immunogenicity test can detect changes in product quality or concentration.

Discussion: Novartis agreed to this request. CBER indicated that means other than (b)(4) may be needed to degrade the vaccine and that degradation to the point at which the test could detect a difference was optimal. In addition, CBER clarified that data testing vaccine lots with known 1/2 or 1/4th potency by concentration would also be helpful. Novartis asked if this testing should be done now or after the assays have been reoptimized. CBER indicated that this testing should be done with the final assay method after completion of the reoptimization and revalidation.

Additional discussion: Novartis asked for clarification on what CBER expected with regard to a response to this IR. CBER said that CBER was requesting a commitment from Novartis to address each of the issues and a rough time line indicating when the work on each item would start. CBER recognizes that responses to the IR comments will include ongoing discussions between Novartis and CBER and Novartis cannot provide completion dates at this time.

Novartis asked when CBER would like to form the Technical Working Group. CBER suggested that Novartis commit to perform these tests and provide the timeline to submit the data to CBER. Once CBER and Novartis had agreed on the overall approach, the details of the collaboration would be worked out. Novartis agreed.

Call ended.