



MEMORANDUM

Date: August 2, 2019

To: STN # 125678/0 (BLA)

From: M. Nahid Parvin, Ph.D.
Laboratory of Biochemistry, Virology and Immunochemistry (LBVI)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

Through: Muhammad Shahabuddin, Ph.D.
Chief, LBVI/DBSQC/OCBQ/CBER/FDA

Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ/CBER/FDA

CC: Bharat Khurana
Chair, DVRPA/OVRR/CBER/FDA

Sudhakar Agnihothram
RPM, DVRPA/OVRR/CBER/FDA

Josephine Resnick
RPM, DVRPA/OVRR/CBER/FDA

Subject: Review of BLA- STN # 125678/0 Analytical Procedure and Method Validation of Infectious Virus Titer by (b) (4) and Identity Assay by (b) (4) of MVA-BN.

Applicant: BAVARIAN NORDIC

Product: MVA-BN Smallpox Vaccine

Recommendation: Acceptable.

1. Review Summary:

Bavarian Nordic A/S submitted their original BLA for the Modified Vaccinia Ankara Bavarian Nordic (MVA-BN) Smallpox Vaccine (liquid-frozen formulation) on October 25, 2018. The

proposed indication is active immunization against smallpox and monkeypox in adults aged 18 years and older. MVA-BN is provided as a single-dose, sterile, liquid-frozen suspension for subcutaneous injection containing a dose of 0.5 mL with at least 0.5×10^8 Infectious Units of MVA-BN. In this review memo, the following analytical procedures and method validations were reviewed which were tested at BN site in (b) (4) (BN-^{(b) (4)}):

- 1) Analytical Procedure and Method Validation of determination of Infectious Virus Titer of MVA-BN by (b) (4) for (b) (4) Drug product.
- 2) Analytical Procedure and Method validation of Identity Assay of MVA-BN by (b) (4) for (b) (4) Drug Product.

Upon review of the information provided by the sponsor, this reviewer concludes that the analytical procedures and method validations of Infectious Virus Titer by (b) (4) and Identity Assay by (b) (4) are suitable for intended use and validated appropriately.

2. Background Summary:

Bavarian Nordic A/S submitted an original BLA application and requested priority review designation (PRD) for the Modified Vaccinia Ankara Bavarian Nordic (MVA-BN) Smallpox Vaccine (liquid-frozen formulation) under Section 351(a) of the PHS Act. Sponsor has developed a proprietary strain of the orthopox virus Modified Vaccinia Ankara Bavarian Nordic (MVA-BN®) as a live, highly-attenuated, non-replicating viral vaccine for protection against smallpox disease. MVA-BN has been developed to address the unmet medical and public health need for attenuated smallpox vaccines for people for whom the currently licensed replicating vaccine ACAM2000, is contraindicated. The vaccine may be used for both primary vaccination of smallpox vaccine-naïve adults and for revaccination of smallpox vaccine-experienced adults. The virus is grown in Chicken Embryo Fibroblast (CEF) cells, harvested and purified in at the manufacturing plant in Kvistgaard, Denmark (BN-K).

During the IND phase, BN relied on the tissue culture infectious dose 50 (TCID₅₀) potency assay for material used in the non-clinical and clinical studies. However, as part of the development of recombinant vaccines, BN developed a (b) (4)-based assay for determination of infectious virus titer and transgene expression. In addition to the potential of this assay to include quantitative analyses of transgene expression, it has advantages over the traditional TCID₅₀ assay for measurement of infectious virus titer. In general, the (b) (4)-based assay is faster, more precise, has a smaller standard deviation and allows a higher throughput. Additionally, the method is more robust as the assay is no longer performed on primary CEF cells but on a (b) (4) which allows better standardization thereby enhancing the control of the quality of the product.

Therefore, BN had submitted an (b) (4) amendment ^{(b) (4)} outlining the proposed strategy to change the potency assay from TCID₅₀ to (b) (4)-based assay. The proposed plan

includes full validation and confirmation of equivalency of the methods and will allow for the use of the (b) (4) -based potency assay as an amendment (b) (4) to (b) (4). BN submitted this (b) (4) to support the development and validation of the manufacturing process for the (b) (4) MVA-BN drug product (DP). BN later submitted the proposal and development and validation reports for (b) (4) -based virus titer assay as an amendment 343 to IND 11596 to support the change of the potency assay for the MVA-BN (b) (4) DP liquid frozen (LF) formulation.

This submission also includes the method to confirm the identity of MVA-BN by (b) (4) and its validation. (b) (4) are used to confirm the identity of MVA-BN which is one of the important characteristics of attenuated MVA-BN virus.

3. Submitted Information Reviewed:

This is an original BLA submission. Information submitted and reviewed includes:

- Section 2.2 Introduction
- Section 3.2.S.4.2 Analytical procedure of Infectious virus titer
- Section 3.2.S.4.3 Appendix 3 Doc. No. 82000942 Method Validation Report for (b) (4) -based (b) (4) of IMVAMUNE/IMVANEX/MVA-BN® and recombinant MVA-BN® using (b) (4)
- Section 3.2.S.4.2 Analytical procedure of Identity
- Section 3.2.S.4.3 Appendix 10 BN0007588 Method Validation Report for Identity Testing of MVA-BN® by (b) (4)
- Section 3.2.S.5 Reference Standards or Materials
- SOP BN003520 (b) (4) -based (b) (4) of MVA-BN® and recombinant MVA-BN® Using (b) (4)
- SOP BN0002649 Identity Testing of MVA-BN® by (b) (4)
- SOP BN0002575 DNA Purification
- Doc. No. 82000969 Comparability Report for Virus Titer Determination of MVA-BN/IMVAMUNE/IMVANEX using TCID₅₀ assay or the (b) (4) -based assay.
- Doc. No. 50000117 Development Report for Assay Transfer of (b) (4) -based (b) (4) of MVA-BN®

4. Review:

4.1 Review of Analytical Procedure for Determination of Infectious Virus Titer:

BN uses (b) (4) to determine the Infectious virus titer for (b) (4) drug product provided in section 3.2.S.4.2.

The reportable titer (log₁₀ Inf.U/mL) of a sample is the average of the (b) (4) replicates.

Assay acceptance criteria:

(b) (4)

[REDACTED]

The method is used for testing of intermediates, release and stability testing of (b) (4) DP. Lot release testing will be performed at the same site (BN-(b) (4)) where validation was performed. However, Sponsor has several DP release testing locations. They need to provide method transfer report if they use different testing location for lot release testing.

Conclusion: The analytical procedure of infectious virus titer is suitable for intended use.

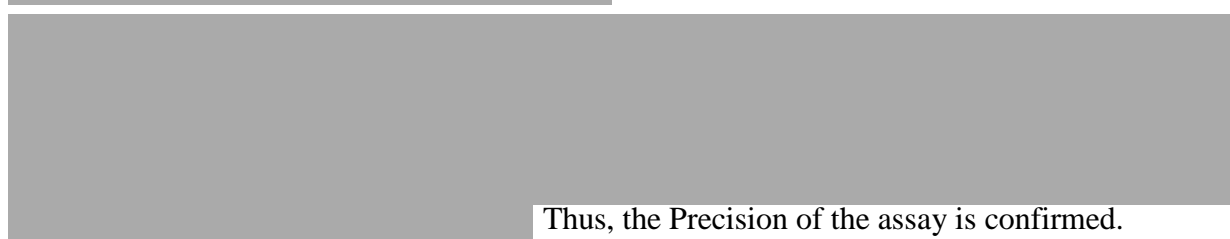


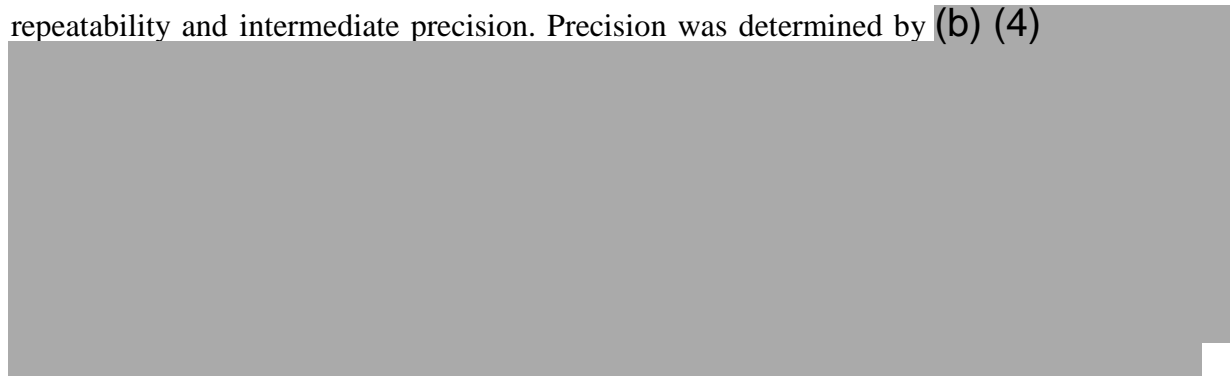
4.2 Review of Validation of Analytical Procedure of Infectious Virus Titer:

Method validation was performed according to a method validation protocol and is documented in method validation report. Per section 3.2.S.4.3-Appendix 3, validation parameters precision, linearity, range, specificity and accuracy were evaluated. The validation was performed with (b) (4)

samples.



Precision is the variability in measurements of multiple samples from a homogeneous sample population tested under normal assay conditions. Precision of the assay was evaluated by

repeatability and intermediate precision. Precision was determined by (b) (4)



Thus, the Precision of the assay is confirmed.

Linearity of an analytical method is the ability within a given range to obtain test results that are directly proportional to the concentration of the analyte in the test sample. Linearity of the assay was evaluated for (b) (4)



(b) (4)

The linearity of the assay in the required working range was therefore confirmed.

Range of an analytical method is the interval between the upper and lower concentration of the analyte in the sample for which a suitable level of precision and linearity are demonstrated.

Linearity testing did cover sample titers over the range for (b) (4) and all acceptance criteria were met.

Precision testing did cover sample titers over the range for (b) (4) FDP (8.29-8.97 log₁₀ Inf.U/mL), (b) (4) all acceptance criteria were met.

(b) (4)

Furthermore, the range of the lower specification limit of (b) (4), the currently obtained maximum concentration of (b) (4) and the

specification of in process controls (b) (4)
(b) (4) are covered by precision and linearity testing.

All validation criteria were covered within this range (b) (4).

Specificity was demonstrated for each assay based on the (b) (4)

(b) (4)
The specificity of the assay was confirmed.

Accuracy: According to the ICH Guideline Q2 (R1) accuracy may be inferred once precision, linearity and specificity were established. Based on the above validation review, precision, linearity and specificity were confirmed. Therefore, accuracy can be inferred from this validation.

During this validation no test deviations occurred.

Conclusion: The validation of the method for determination of infectious virus titer is acceptable.

4.3 Review of Analytical Procedure for Identity Assay

Per section 3.2.S.4.2 Appendix 2, BN uses the Identity assay for release testing of MVA-BN (b) (4) DP. These assays are performed at BN-^{(b) (4)} site. The attenuated phenotype of the Vaccinia MVA strain is based (b) (4)

(b) (4). The identity assay is based on characterization of the MVA-BN genome by (b) (4)

(b) (4) are also included which are routinely used to generate recombinant MVA-BN derived products.

Per SOP BN0002649, Viral DNA from MVA-BN (b) (4) DP are used as test samples. (b) (4) is used as a positive control. Viral DNA test samples from MVA-BN (b) (4) FDP are prepared according to SOP BN0002575. (b) (4)

(b) (4)

The assay acceptance criteria include (b) (4)

Conclusion: The assay is suitable for its intended use.

4.4 Review of Validation of Identity Assay

The assay was validated in the same laboratory where it will be performed as a release test. The identity assay is entirely qualitative, therefore only specificity of the method is evaluated according to ICH guideline summarized in section 3.2.S.4.3 Appendix 10.

Specificity is defined as the ability to assess the analyte unequivocally in the presence of components which may be expected to be present. (b) (4) was used as identification test to (b) (4)

(b) (4) DP (Lot#(b) (4)) were tested in the validation assay. (b) (4) was tested as negative control and (b) (4) were detected, which confirmed that the (b) (4) test conditions are specific for (b) (4). DP Lot# (b) (4) was tested as a positive control. (b) (4) this batch was verified during method development by (b) (4) and was demonstrated to be appropriate for the intended use as positive control.

(b) (4) test run was considered sufficient during method validation and was performed according to SOP BN0002649. All (b) (4) passed the acceptance criteria which is (b) (4)

The validation of the identity test was completed successfully. The specificity of the assay was confirmed.

Conclusion: The method validation of Identity assay is acceptable.

5. CBER Information Request and Review:

The following information request was submitted to the sponsor on November 20, 2018. The response was received on November 26, 2018.

CBER IR: Information request for STN 125678/0 Bavarian Nordic original BLA for the following Analytical Procedure

1) Infectious virus titer:

- a) Please provide a copy of SOP (BN0003431) for propagation and cell banking of (b) (4) cells

2) Identity:

- a) Please provide a copy of SOP (BN0002649, v 6.0) for Identity testing of MVA-BN by (b) (4)

Sponsor Response:

The requested SOPs are provided and included in Section 3.2.S.4.2.

Review of Response:

The sponsor's response is acceptable.

6. Conclusion:

Based on the data reviewed, the analytical procedures and validation of analytical procedures of (1) “(b) (4) -based Titration of Infectious Virus titer of MVA-BN and recombinant MVA_BN using (b) (4)” (specifically validated for MVA-BN) and (2) Identity testing of MVA-BN by (b) (4) are acceptable.