Our STN: BL 125678/0 **BLA APPROVAL**

Bavarian Nordic A/S
Attention: Renee Boerner, PhD
3025 Carrington Mill Boulevard
Morrisville, NC 27560

September 24, 2019

Dear Dr. Boerner,

Please refer to your Biologics License Application (BLA) submitted October, 25, 2018, received October 25, 2018, under section 351(a) of the Public Health Service Act (PHS Act) for Smallpox and Monkeypox Vaccine, Live, Non-replicating.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2096 to Bavarian Nordic A/S, Hejreskovvej 10A, 3490 Kvistgaard, Denmark, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the liquid-frozen suspension of Smallpox and Monkeypox Vaccine, Live, Non-replicating, which is indicated for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): NCT01144637, NCT00189943, NCT00316524, NCT00686582, NCT00857493, NCT00316589, NCT00082446, NCT01913353, NCT00189917, NCT00316602, NCT02038881, NCT01668537, NCT00189956, NCT00189904, NCT00565929, NCT00437021, NCT00879762, NCT00914732, NCT01827371, NCT03472014, NCT00189930, NCT00390078.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Smallpox and Monkeypox Vaccine, Live, Non-replicating drug substance at Bavarian Nordic A/S, Hejreskovvej 10A, 3490 Kvistgaard, Denmark. The final formulated product will be manufactured at (b) (4), labeled and packaged at (b) (4).
You may label your product with the proprietary name JYNNEOS and market it in 0.5 mL single-dose vials.

We did not refer your application to the Vaccines and Related Biological Products Advisory Commitee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for Smallpox and Monkeypox Vaccine, Live, Non-replicating shall be 36 months from the date of manufacture when stored at -25 °C to -15°C and (b) (4) from the date of manufacture when stored at (b) (4). The date of manufacture shall be defined as the date of formulation of the final bulk of the drug product. The dating period for your drug substance shall be (b) (4) when stored at (b) (4). We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Smallpox and Monkeypox vaccine, live, non-replicating, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 60, dated Septmeber 20, 2019, and the draft carton labeling submitted under amendment 61, dated September 24, 2019, and container labeling submitted under amendment 59, dated September 20, 2019.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on September 24, 2019 and September 20, 2019, respectively, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN 125678 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a material threat medical countermeasure priority review voucher, as provided under section 565A of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 125678. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a material threat medical countermeasure priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "**Notification of Intent to Submit an Application with a Material Threat Medical Countermeasure Priority Review Voucher**."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher.

For additional information regarding the priority review voucher, see FDA's draft guidance, *Material Threat Medical Countermeasure Priority Review Voucher Program* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/material-threat-medical-countermeasure-priority-review-vouchers-draft-guidance-industry. This guidance when finalized, will represent the current thinking of FDA on this topic.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable since smallpox has been eradicated and pediatric populations at risk of monkeypox are limited to small and dispersed communities living in areas lacking sufficient infrastructure and stability to support clinical trials.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval.

Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Marion Gruber, PhD
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research