

**Date:** September 12, 2019

**From:** Marion F. Gruber, PhD, Director, Office of Vaccines Research & Review

**STN:** 125678/0 Jynneos, smallpox vaccine, live, non-replicating, modified vaccinia virus Ankara

**Subject:** Justification for deviating from the guidance entitled “Submitting Separate Marketing Applications and Clinical data for Purposes of Assessing User Fees” (December 2004)

On October 25, 2018, Bavarian Nordic (BN) submitted a BLA for Jynneos, smallpox vaccine, live, non-replicating, modified vaccinia virus Ankara. The indication proposed by the sponsor at that time was “for active immunization against smallpox in adults aged 18 years and older.” On February 14, 2019 and March 5, 2019, CBER requested for BN to include an additional indication for this product, i.e., “prevention of monkeypox disease in adults aged 18 years and older.” The FDA approved indication is “prevention of smallpox or monkeypox disease in adults 18 years and older determined to be at high risk for smallpox or monkeypox infection.”

The FDA guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (December 2004) states “If submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration (or otherwise consistent with sections II.A.2 and II.A.3, above) can be regarded, for the purposes of assessing user fees, as one application regardless of the dose to be administered; the duration of use; the schedule of administration; the population in which the product is indicated; or the condition for which the product is indicated. The guidance also states “after initial submission, a pending original or supplemental application should not be amended to add a new indication or claim” and furthermore “If the original application is not yet approved, a request for approval of other new indications or claims should be submitted in a separate, original application. If the initial application is approved, the application can be subsequently supplemented to add a new indication (See section II.B. on supplemental applications.) At the time of submission, an original application should be complete and ready for a comprehensive review.”

Good guidance practice (GGP) regulations at 21 CFR 10.115(d)(3) permit FDA to depart from guidance documents “only with appropriate justification and supervisory concurrence.”

The following provides my justification for deviating from the above cited FDA guidance:

1. Smallpox and monkeypox are caused by variola and monkeypox viruses, respectively. Both are orthopox viruses belonging to the poxviridae family. Combined clinical and non-clinical data contained in the original BLA submission for Jynneos suggest that Jynneos elicits protective immunity against orthopox viruses in general. The agency requested for the monkeypox indication to be included into the prescribing information because monkeypox outbreaks have been observed repeatedly in humans in West- and Central Africa, particularly in the Democratic Republic of the Congo and in Nigeria (Durski, 2018, McCullun, 2014). Outside of Africa, occurrences of monkeypox infection have occurred in 2018 in travelers from Nigeria (Erez, 2019). In the US, one monkeypox outbreak was reported in 2003 as a result of rodent importation from AFRICA (Reed, 2004). There is currently no licensed vaccine to protect against monkeypox. The review team noted, and I concur, that the data contained in the original BLA submission support this second indication and address an important public health need, i.e., providing an effective countermeasure to protect persons at high risk for monkeypox infection.
2. The review team noted, and I concur, that the data submitted with the original BLA application for Jynneos was sufficient to support this second indication, i.e., prevention of monkeypox disease in adults 18 years of age and older. The effectiveness of Jynneos for the prevention of monkeypox is inferred from the antibody responses in clinical study participants and the studies in non-human primates that showed prior vaccination with Jynneos protected animals from lethal monkeypox challenge (relevant sections of the Jynneos package insert are 13.2 Animal Toxicology and/or Pharmacology and 14.1 Vaccine Effectiveness).
3. The request to include a second indication, i.e., prevention of monkeypox disease in adults 18 years of age and older was made by the agency, not the applicant, during the review cycle for STN 125678/0 in order to make available an effective countermeasure against outbreaks of monkeypox.

## References

Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees December 2004- Guidance for industry

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-separate-marketing-applications-and-clinical-data-purposes-assessing-user-fees>

21 CFR 10.115(d)(3) Good Guidance Practices

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=10.115>

McCollum *et al*, 2014. Human monkeypox, *Clin. Inf. Dis.* 58, 260-7

Durski *et al*, 2018. Emergence of monkeypox-West and Central Africa,1970-2017, *MMWR Morb. Mortal. Wkly Rep*, 67, 306-310

Erez *et al* 2019. Diagnosis of Imported monkeypox, Israel, 2018 *Emerg.Infect. Dis.* 25, 980-983

Reed *et al*, 2004., The detection of monkeypox in humans in the Western Hemisphere. *N. Engl. J. Med.*, 350, 342-50