Review Memorandum

Date:	**December 23, 2024**
To:	**The File**
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Through:	**David C. Kaslow, MD, OVRR**
Applicant name:	**National Institute for Allergy and Infectious Diseases (NIAID)**
EUA Application Number:	**28801**
Product:	**JYNNEOS (Smallpox and Mpox Vaccine, Live, Non-replicating)**
Subject:	**Revision of JYNNEOS Letter of Authorization**

On August 9, 2022, pursuant to Section 564 of the Federal Food, Drug & Cosmetic Act, FDA issued an emergency use authorization (EUA) of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) to authorize the administration of: (i) two doses (0.1 mL each) of JYNNEOS 4 weeks apart by the intradermal (ID) route of administration to individuals 18 years and older determined to be at high risk for monkeypox infection; and (ii) two doses (0.5 mL each) of JYNNEOS 4 weeks apart by the subcutaneous (SC) route of administration to individuals younger than 18 years of age determined to be at high risk for monkeypox infection. This memorandum provides an executive summary, review, and recommendations for reissuing the letter of authorization to 1) revise condition J of the letter of authorization to provide flexibility to determine a different reporting interval for periodic safety reports, if appropriate; 2) remove the requirement that under the emergency use authorization JYNNEOS must be supplied by the Administration for Strategic Preparedness and Response (ASPR); and 3) revise the Fact Sheets to align with the currently approved U.S. Package Insert (see Section II.G of this memorandum). In doing so, this review memorandum also addresses the basis for FDA's continued emergency use authorization of JYNNEOS for the administration of:

1) two doses (each 0.1 mL dose containing 2 x 10^7 $TCID_{50}$ of MVA-BN, hereafter referred to as 0.1 mL) of JYNNEOS 4 weeks apart by the ID route of administration to individuals 18 years of age and older determined to be at high risk for mpox infection; and
2) two doses (each 0.5 mL dose containing 1 x 10^8 $TCID_{50}$ of MVA-BN, hereafter referred to as 0.5 mL) of JYNNEOS 4 weeks apart by the SC route of administration to individuals under 18 years of age determined to be at high risk for mpox infection.

In addition, the authorization will extend storage of certain lots of JYNNEOS at 2-8°C for up to 8 weeks after thawing. *See* Letter of Authorization (December 20, 2024), and the footnote[1] in Section 2.2 and Section 16.1 of the

[1] Only certain lots may be held at 2-8ºC for 8 weeks. To confirm that a given lot may be held at +2°C to +8°C for 8 weeks , please verify that the lot is listed on this web page: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-

Fact Sheets for Healthcare Providers Administering Vaccine.

I. EXECUTIVE SUMMARY

Mpox, formerly called monkeypox, is caused by monkeypox virus (MPXV), an orthopoxvirus related to variola virus (smallpox). The first human case of mpox[2] was recorded in 1970. Mpox which is spread through close, personal contact often manifests as painful lesions in the genital region that can take two to three weeks to completely heal and has been associated with sporadic outbreaks over the past decades, often in international travelers who had visited the African continent. The most recent global outbreaks of mpox began in May 2022. Outbreaks in the U.S. were reported from May through August 2022.[3,4] Through September 30, 2024, a total of 109,699 confirmed mpox cases and 236 deaths have been reported from 123 countries.[5] The majority of recent cases have occurred in Africa (9,320 confirmed cases and 34 confirmed deaths in 2024), driven by a large outbreak in the Democratic Republic of Congo (7,634 confirmed cases and 25 confirmed deaths).[3] The World Health Organization (WHO) reported 2,763 confirmed cases during September 2024, the highest monthly total since November 2023. This recent peak in cases was driven primarily by the large outbreak in Africa caused by Clade Ib MPXV and an increasing outbreak of Clade IIb mpox among Australian men who have sex with men[5].

The first case of Clade Ib mpox in the United Stated (U.S.) was reported on November 16, 2024, in San Mateo County, south of San Francisco, California (CA). CDC worked with the state health department to identify potential contacts.[6] Of note, Clade Ib MPXV is a current clade of concern, which prompted WHO and Africa CDC to declare the outbreak an international public health emergency in August 2024.[7] Although there is currently no evidence of Clade Ib MPXV circulating in U.S. communities, mpox poses a significant public threat to adult and pediatric populations both globally and in the U.S. Because children accounted for numerous mpox cases in the most recent Clade Ib mpox outbreak, there is an increased concern about the risk of mpox in children in the U.S.[8] and globally.

JYNNEOS is a U.S.-licensed vaccine, approved for prevention of smallpox and mpox disease in adults 18 years of age and older who are determined to be at high risk for smallpox or mpox infection. It is a live virus vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus, that was originally developed for use in the event of a smallpox bioterrorist attack in certain populations (e.g., immunocompromised individuals). JYNNEOS is approved for use as a 2-dose (0.5 mL each) regimen administered by subcutaneous injection with the doses given 4 weeks apart. For detailed information, please refer to JYNNEOS U.S. Package Insert.

JYNNEOS was in limited supply during the July through August 2022 outbreak. In response to the 2022 outbreak, on August 9, 2022, pursuant to Section 564 of the Federal Food, Drug & Cosmetic Act, FDA issued an emergency use authorization (EUA) of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating) to

regulatory-and-policy-framework/expiration-dating-extension#mpoxvaccine. If the lot number is not identified as being eligible for the 8-week hold time on this page, then the vaccine may only be kept at +2°C to +8°C (+36°F to +46°F) for 4 weeks.

[2] On November 28, 2022, following a series of consultations with global experts, the World Health Organization (WHO) began using a new preferred term "mpox" as a synonym for monkeypox, the disease caused by the monkeypox virus. Refer to: https://www.who.int/news/item/28-11-2022-who-recommends-new-name-for-monkeypox-disease

[3] Ongoing Clade II mpox global outbreak

[4] WHO mpox outbreak

[5] 2022-24 Mpox Outbreak: Global Trends

[6] California confirms first clade I mpox case

[7] WHO declares mpox (sic) virus a public health emergency of international concern | UN News

[8] Clade I Monkeypox outbreak originating in Central Africa

authorize the administration of: (i) two doses (0.1 mL each) of JYNNEOS 4 weeks apart by the ID route of administration to individuals 18 years and older determined to be at high risk for monkeypox infection; and (ii) two doses (0.5 mL each) of JYNNEOS 4 weeks apart by the SC route of administration to individuals younger than 18 years of age determined to be at high risk for monkeypox infection. This EUA was supported by the totality of evidence available, including from 1) results of a Phase 2 study (NIAID DMID Protocol 09-0002; NCT05512949); 2) available JYNNEOS safety and immunogenicity data in adults; and 3) historical data from the use of live vaccinia virus smallpox vaccine in pediatric populations. For further details on data supporting this EUA, please refer to the EUA memorandum dated August 9, 2022. Subsequently, on August 16, 2022, JYNNEOS EUA issued a granting letter to extend the storage of thawed JYNNEOS drug product (DP) at 2-8°C for up to 8 weeks for product that had been stored in the Strategic National Stockpile (SNS) and was distributed by the Administration for Strategic Preparedness and Response under the authorization.

The global incidence of Clade Ia mpox and the ongoing outbreak of Clade Ib mpox in Africa with the recent detection of the first Clade Ib mpox case in the U.S. underscores the importance of immunization both globally and in the U.S. There continues to be a limited supply of JYNNEOS available globally and in the U.S. Approximately 4 million people are currently estimated to be at elevated risk of mpox in the U.S. and may need vaccination, including those eligible for pre-exposure prophylaxis with medications to prevent human immunodeficiency virus (HIV). Therefore, several million doses of JYNNEOS are required to immunize that population and only limited number of doses are estimated to be in U.S. distribution. In addition to the limitations on the supply of JYNNEOS, individuals under 18 years of age are increasingly being exposed to MPXV and are in need of post-exposure prophylaxis. Although another vaccine (ACAM 2000) is approved for use in prevention of mpox, the adverse reactions associated with ACAM2000 (as illustrated by a boxed warning on its labeling) means that its use may not be appropriate for all individuals determined to be at high risk for mpox infection (see ACAM 2000 USPI for further details).

Taken together, there is an increased need to continue the emergency use of JYNNEOS, both the dose-sparing ID regimen in adults and the SQ dosing regimen in individuals under 18 years of age, given the current global epidemiology and clear and present risk of new U.S. mpox outbreaks. Furthermore, the August 9, 2022, EUA was limited to use of JYNNEOS doses supplied only by ASPR from the SNS. Due to changed circumstances, we conclude that this limitation on distribution is no longer necessary or appropriate to protect the public health. Whereas there was previously a need for ASPR to coordinate across federal, state, and local government entities to ensure appropriate allocation of the vaccines and ASPR also maintained all the domestic supply of JYNNEOS, this is no longer the case.

Since FDA's 2022 EUA, data have accrued demonstrating the continued effectiveness of JYNNEOS, administered by the ID route, in protection against mpox. Observational studies conducted by CDC in individuals 18 through 49 years of age (men who have sex with men, transgender adults) suggest that administration of JYNNEOS (through dose-sparing or the approved route of administration) by any route provides comparable protection against mpox[9] (refer to Section II.D). Results from these observational studies were further verified in a clinical trial (NCT05512949) sponsored by NIAID and reported at the European Society of Clinical Microbiology and Infectious Diseases Global Congress in Barcelona in April 2024[10] (refer to Section II.D). Further evidence demonstrating effectiveness of JYNNEOS administered by the ID route in protection against mpox comes from a CDC real-world data assessment of vaccine effectiveness (VE) of JYNNEOS conducted

[9] Estimated Effectiveness of JYNNEOS Vaccine in Preventing Mpox: A Multijurisdictional Case-Control Study — United States, August 19, 2022–March 31, 2023 | MMWR

[10] Lower dose of mpox vaccine is safe and generates six-week antibody response equivalent to standard regimen | National Institutes of Health (NIH)

during the 2022 mpox outbreak. The reported VE was an adjusted 75.2% for dose-sparing vaccination and 85.9% for approved route of vaccination. These results demonstrating the effectiveness of the emergency use of JYNNEOS for ID route are consistent with multiple previous studies evaluating vaccine effectiveness (VE) [11,12,13] of JYNNEOS and strengthen the evidentiary basis supporting continued emergency use of JYNNEOS for protection against mpox. Based on the totality of evidence, it is reasonable to expect that the known and potential benefits of administering two doses (0.1 mL each) of JYNNEOS administered 4 weeks apart by the ID route of administration to individuals 18 years of age and older determined to be at high risk for mpox infection for prevention of mpox disease outweigh the known and potential risks for those individuals.

In support of SC administration of two doses (0.5 mL each) of JYNNEOS to individuals younger than 18 years of age, FDA considers the available JYNNEOS safety and immunogenicity data in adults as well as the historical data with use of live vaccinia virus smallpox vaccines in pediatric populations. The overall favorable safety profile following administration of JYNNEOS under hundreds of new emergency individual patient IND requests for post-exposure prophylaxis in children ranging from a few months of age through the teenage years, also contributes to the evidentiary basis for JYNNEOS use in individuals younger than 18 years of age.

This EUA action also includes revision of the LOA to modify condition J of the LOA to provide flexibility in the reporting interval for periodic safety reports (PSRs). Based on the review of postmarketing reports, mpox case trends, and vaccine administration trends, the Office of Biostatistics and Pharmacovigilance (OBPV) has determined that having flexibility to modify the reporting interval for PSRs would be of value. Please refer to Section II.F for rationale of such determination.

Based on the totality of evidence available, the review team concludes that the known and potential benefits of two doses (0.1 mL each) of JYNNEOS 4 weeks apart by the ID route of administration to individuals 18 years of age and older determined to be at high risk for mpox infection for the prevention of mpox disease, continues to outweigh the known and potential risks for those individuals. Additionally, based on the totality of evidence available, the review team also concludes that the known and potential benefits of two doses (0.5 mL each) of JYNNEOS 4 weeks apart by the SC route of administration to individuals younger than 18 years of age determined to be at high risk for mpox infection for the prevention of mpox disease, continues to outweigh the known and potential risks for those individuals. In addition, the review team concludes that these emergency uses may be effective. Furthermore, based on the review of postmarketing reports, mpox case trends, and vaccine administration trends, it is appropriate to modify the reporting interval requirements for PSRs to provide flexibility. In addition, it is appropriate to no longer require that the emergency uses covered by the authorization are supplied by ASPR.

Taken together, the review team recommends: 1) removing the requirement that under the emergency use authorization JYNNEOS must be supplied by ASPR; 2) authorizing the continued use of: (a) two doses (0.1 mL each) of JYNNEOS administered intradermally 4 weeks apart for prevention of mpox disease in individuals 18 years of age and older determined to be at high risk for mpox infection; and (b) two doses (0.5 mL each) of JYNNEOS administered subcutaneously 4 weeks apart for prevention of mpox disease in individuals younger

[11] Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. Nat Med 2023;29:748–52. https://doi.org/10.1038/s41591-023-02229-3 PMID:36720271

[12] Payne AB, Ray LC, Cole MM, et al. Reduced risk for mpox after receipt of 1 or 2 doses of JYNNEOS vaccine compared with risk among unvaccinated persons—43 U.S. jurisdictions, July 31–October 1, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1560 – 4 https://doi.org/10.15585/mmwr.mm7149a5 PMID:36480479

[13] Deputy NP, Deckert J, Chard A, et al. JYNNEOS vaccine effectiveness against mpox disease in the U.S. N Engl J Med Epub May 18, 2023. https://www.nejm.org/doi/10.1056/NEJMoa2215201

than 18 years of age determined to be at high risk for mpox infection; 3) revision to the Fact Sheets to align with the U.S. Package Insert (see Section II.G of this memorandum) and 4) revising Condition J of the letter of authorization (LOA) to provide flexibility in the reporting interval for PSRs.

Safety surveillance under the oversight of FDA and CDC will continue to actively and passively monitor for risks of local and systemic side effects and other known and unknown short-term and long-term risks of the authorized vaccine.

II. REVIEW

A. Disease Background

Monkeypox virus (MPXV) is an orthopoxvirus related to smallpox.[14] MPXV was discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research. Despite the name "monkeypox virus," the original source of the disease remains unknown. Sources of human infection include African rodents and non-human primates. Currently, two clades of MPXV circulate: Clade I and Clade II. The two clades cannot be distinguished by clinical presentation, e.g., by examination of lesions. Rather, laboratory diagnosis is required, first as to MPXV as the etiologic agent and then by clade assessment. Each clade of the virus has subclades, Clade Ia and Clade Ib; Clade IIb. Outbreaks from different subclades can have different characteristics, including who is affected, how the subclade spreads, and what the case fatality rate is.

The first human case of mpox was recorded in 1970. MPXV infections have been associated with sporadic outbreaks for several decades, often in international travelers who have visited the African continent. An international outbreak involving 122 countries that began in early 2022 was associated with the less virulent Clade IIb MPXV. It primarily affected men who have sex with men and their intimate contacts, and the disease often manifested as painful pustular lesions in the genital region that took two to three weeks to completely heal. Of note, these lesions have very high infectious virus titers and until lesions completely heal individuals can potentially spread the virus to others. Although disease caused by Clade IIb MPXV is generally self-limited, in some cases serious illness result and the case fatality rate is estimated at 1%. Death appears to be more common in young children and individuals with immunocompromising conditions. It is unclear whether antiretroviral therapy modifies the risk of death from mpox in those with HIV.[15]

The global outbreak of mpox began in May 2022 was predominantly associated with the Clade IIb MPXV and consequential Clade IIb mpox outbreaks in U.S. were reported from May through August of 2022.[1,2] The current outbreak of mpox in Africa is associated with Clade Ib and the majority of African mpox cases are reported in the Democratic Republic of the Congo (DRC), where clade Ib spread is driven by close interpersonal human-to-human contact. The current clade Ib outbreak from DRC is expanding into neighboring Burundi and Uganda causing significant and expanding outbreaks. Outside these 3 African countries, recent cases have been reported in Zimbabwe, South Africa, Côte d'Ivoire, Tanzania, Kenya, and Uganda. Outside of Africa, Clade Ib has been seen in Sweden[16], Thailand.[17]

During the month of September 2024 alone, 2,763 confirmed cases were reported to the WHO. This is the

[14] See Moore MJ, Rathish B, Zahra F. Mpox.StatPearls, Last update July 16, 2022; https://www.ncbi.nlm.nih.gov/books/NBK574519/, last accessed August 7, 2022.
[15] Thornhill JP, Barkati S, Walmsley S et al. Mpox Virus Infection in Humans across 16 Countries — April–June 2022. N Engl J Med, July 21, 2022, https://www.nejm.org/doi/full/10.1056/NEJMoa2207323.
[16] Sweden reports first clade 1 mpox case outside of Africa as NIH shares disappointing Tpoxx results | CIDRAP
[17] More global mpox spread as clade Ib confirmed in Thailand, the 2nd case outside Africa | CIDRAP

highest monthly total since November 2023 and driven primarily by an outbreak of Clade Ib mpox in Africa, India[18], Germany,[19] and just recently the United Kingdom.[20] Concern about the ever-expanding outbreak of Clade Ib mpox is driven primarily by the increased fatality rate that can accompany this clade, reported to be up to 10% in some settings.

The first case of Clade Ib mpox in the U.S. was reported on November 16, 2024, in San Mateo county, south of San Francisco, CA and CDC worked with the state health department to identify potential contacts.[21] Of note, Clade Ib mpox, which is the current clade of concern, prompted WHO and Africa CDC to declare the outbreak an international public health emergency in August 2024.[22] Although there is currently no evidence of Clade Ib mpox circulation in U.S. communities, mpox poses a significant public threat to adult and pediatric populations both globally and in the U.S. Because children accounted for numerous mpox cases in the most recent Clade Ib mpox outbreak, there is an increased concern about the risk of mpox in children in the U.S.[1] and globally.

B. JYNNEOS for the Prevention of Mpox

JYNNEOS is a U.S.-licensed vaccine approved for prevention of smallpox and mpox disease in individuals 18 years of age and older who are determined to be at high risk for smallpox or mpox infection. It is a live, non-replicating vaccine using Modified Vaccinia Ankara (MVA) virus that was originally developed for use in the event of a smallpox bioterrorist attack in certain populations (e.g., immunocompromised individuals). JYNNEOS is approved for use as a 2-dose (0.5 mL each) regimen administered by SC injection with the doses given 4 weeks apart. For detailed information, please refer to JYNNEOS U.S. Package Insert.

C. Requirements for EUA

The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of threats. On August 9, 2022, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the Secretary of HHS determined that there is a public health emergency, or the significant potential for a public health emergency, that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes mpox. On the basis of such determination, on August 9, 2022, the Secretary then declared that circumstances exist justifying the authorization of emergency use of vaccines during the mpox outbreak, pursuant to section 564(b)(1) of the FD&C Act.[23]

Following the Secretary's EUA declaration, under section 564(c) of the FD&C Act, FDA may issue an EUA related to monkey pox after FDA concludes that the following statutory requirements are met:

- The agent referred to in the August 9, 2022, EUA declaration by the Secretary of HHS (monkeypox virus) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well- controlled

[18] India reports imported clade Ib mpox case | CIDRAP
[19] Germany reports first mpox case from new clade | CIDRAP
[20] UK reports imported clade Ib mpox case | CIDRAP
[21] California confirms first clade I mpox case
[22] WHO declares mpox virus a public health emergency of international concern | UN News
[23] U.S. Department of Health and Human Services, Determination of Public Health Emergency or Significant Potential for a Public Health Emergency and Declaration that Circumstances Exist Justifying an Authorization Pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.

trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by MPXV , or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by MPXV.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved uses of approved medical products (or unapproved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents.

An EUA will remain in effect until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products is terminated under section 564(b)(2) of the FD&C Act or the EUA is revoked under section 564(g) of the FD&C Act. Section 564(g) provides that "[t]he Secretary shall periodically review the circumstances and the appropriateness of an authorization" under section 564. In addition, section 564(g)(2) states the Secretary "may revise or revoke an authorization" if:

- the circumstances described under [section 564(b)(1)] no longer exist;
- the criteria under [section 564(c)] for issuance of such authorization are no longer met; or
- other circumstances make such revision or revocation appropriate to protect the public health or safety.

Consistent with these provisions and section 564(g)(1) of the FD&C Act, FDA periodically reviews the circumstances and appropriateness of an EUA and revises or revokes an EUA if the criteria in section 564(g)(2) is met and if certain circumstances exist.

D. Observational Studies of the Effectiveness of JYNNEOS Dose Sparing

Because information on JYNNEOS vaccine effectiveness (VE) was limited, a matched case-control study was conducted by CDC to evaluate VE against mpox among men who have sex with men and transgender adults aged 18 through 49 years.[9] During August 19, 2022, through March 31, 2023, a total of 309 case-patients were matched to 608 control patients. Adjusted VE was 75.2% (95% CI: 61.2 - 84.2) for partial vaccination (1 dose) and 85.9% (95% CI: 73.8 - 92.4) for full vaccination (2 doses). Adjusted VE for full vaccination by subcutaneous, intradermal, and heterologous routes of administration was 88.9% (95% CI: 56.0 - 97.2), 80.3% (95% CI: 22.9 - 95.0), and 86.9% (95% CI: 69.1 - 94.5), respectively[9]. This study was the first to estimate VE following dose sparing by route of administration. Similar point estimates and overlapping CIs for estimates by route of administration suggest that vaccine administration by any route provides comparable protection against mpox. The results are consistent with those from multiple previous studies evaluating vaccine performance or effectiveness[4 - 6] and strengthens the evidentiary basis that supports dose sparing by the ID route of administration of JYNNEOS for prevention mpox disease in adults 18 years of age and older determined to be at high risk for mpox infection.

The dose sparing results were further verified in a clinical trial (NCT05512949) sponsored by NIAID and reported at the European Society of Clinical Microbiology and Infectious Diseases Global Congress in Barcelona in April 2024. Two hundred and twenty-five individuals 18 to 50 years of age who had not previously been vaccinated against mpox or smallpox were enrolled in the study. Participants were randomized to receive either the standard

FDA-approved MVA-BN SC regimen, an ID regimen containing one-fifth of the standard dose, or an ID regimen with one-tenth of the standard dose. Two weeks after the second dose (study day 43), participants who received one-fifth of the standard dose by the ID route had antibody levels equivalent to those of participants receiving the standard MVA-BN regimen by the SC route, based on predefined criteria. By study day 57, participants who received one-fifth of the standard dose by the ID route had lower antibody levels than those in the standard regimen arm by the SC route; the clinical significance of this difference is unknown, particularly given the opportunity for an anamnestic immune response supported by the recently reported mean infection-to-onset incubation period of approximately 8 days[24]. Participants who received one-tenth of the standard dose had inferior antibody levels at all measurements[7]. The results are consistent with those from multiple previous studies evaluating vaccine effectiveness (VE) [25,26,27] of JYNNEOS and strengthens the evidentiary basis that supports the dose sparing (0.1mL) by the ID route of administration of JYNNEOS for prevention mpox disease in adults 18 years of age and older determined to be at high risk for mpox infection.

Together, these studies support the review team's conclusion that that the known and potential benefits of administering two doses (0.1 mL each) of JYNNEOS 4 weeks apart by the ID route of administration to individuals 18 years of age and older determined to be at high risk for mpox infection for prevention of mpox disease, outweigh the known and potential risks for those individuals and that this use may be effective.

E. Review of JYNNEOS for Administration to Individuals Under 18 Years of Age

FDA has reviewed hundreds of emergency individual patient IND requests for post-exposure prophylaxis in children ranging from a few months of age through the teenage years. To date, there have been no safety signals of concern reported to the agency following JYNNEOS administered to these individuals under 18 years of age. In addition, safety surveillance data since the issuance of the 2022 EUA has not identified any major safety concerns on the use of JYNNEOS in individuals under 18 years of age[28]. FDA has also considered the available JYNNEOS safety and immunogenicity data in adults as well the data with use of smallpox vaccines used historically in pediatric populations. The benefit-risk profile of administering JYNNEOS intradermally to pediatric populations is less established than for adults because the study of intradermal administration involved adults only. Additionally, there may be practical challenges in the intradermal route of administration particularly in the youngest pediatric patients.

Based on the totality of evidence available, the review team concludes that the known and potential benefits of administering two doses (0.5 mL each) of JYNNEOS 4 weeks apart by the SC route of administration to individuals younger than 18 years of age determined to be at high risk for mpox infection for prevention of mpox, outweigh the known and potential risks for those individuals. In addition, such use may be effective.

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[24] Ponce L, Linton NM, Toh W, Cheng H, Thompson RN, Akhmetzhanov AR, et al. Incubation Period and Serial Interval of Mpox in 2022 Global Outbreak Compared with Historical Estimates. Emerg Infect Dis. 2024;30(6):1173-1181. https://doi.org/10.3201/eid3006.231095

[25] Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. Nat Med 2023;29:748–52. https://doi.org/10.1038/s41591-023-02229-3 PMID:36720271

[26] Payne AB, Ray LC, Cole MM, et al. Reduced risk for mpox after receipt of 1 or 2 doses of JYNNEOS vaccine compared with risk among unvaccinated persons—43 U.S. jurisdictions, July 31–October 1, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1560 – 4 https://doi.org/10.15585/mmwr.mm7149a5 PMID:36480479

[27] Deputy NP, Deckert J, Chard A, et al. JYNNEOS vaccine effectiveness against mpox disease in the U.S. N Engl J Med Epub May 18, 2023. https://www.nejm.org/doi/10.1056/NEJMoa2215201

[28] Safety Monitoring of JYNNEOS Vaccine During the 2022 Mpox Outbreak — United States, May 22–October 21, 2022, | MMWR

F. Revision of Condition J to Introduce Flexibility to Change Reporting Interval for PSRs

The PSRs contain sponsor assessment of aggregate postmarketing safety data for a specified reporting interval. Following the initial EUA issuance in August 2022, FDA required PSRs to be submitted at monthly intervals.

OBPV has determined that having flexibility to modify the reporting interval for PSRs based on review of postmarketing reports, mpox case trends, and vaccine administration trends would be of value. OBPV's rationale for the change includes the following:

- As of January 09, 2024, and up until July 2024, more than 1,286,849 doses of JYNNEOS had been administered in the U.S.[29].
- By January 2023, the weekly number of doses of JYNNEOS administered in the U.S. had dropped from a high of over 109,000 in August 2022 to less than 5,000 and remained below that level through January 9, 2024.
- The 7-day moving average number of mpox cases per day fell from a high of 467 on August 6, 2022, to below 12 by the end of 2022 and has remained below 12 through August 1, 2024[30].
- A total of 23 monthly periodic adverse experience reports, providing a comprehensive safety data assessment have been reviewed covering the period from August 9, 2022 to July 8, 2024.
- Subsequent to revision of the JYNNEOS package insert on September 29, 2023[31] to include new safety information, no new safety signals or concerns have been identified.
- Flexibility would allow OBPV to modify reporting intervals, when appropriate, to align with data lock points for Periodic Benefit-Risk Evaluation Reports (PBRER) already being completed by Bavarian Nordic A/S.
- While this revision allows for the submission of PSRs for a reporting period of monthly or another appropriate interval determined by OBPV, it is important to note that there will be no change to the content of the periodic safety report or ongoing pharmacovigilance activities. Manufacturer, FDA, and CDC are conducting continuous vaccine safety monitoring and there are no changes to the ongoing active and passive surveillance activities.

Finally, it is important to note that FDA may change the periodicity of reporting intervals as needed. Consideration for a change to the reporting interval may be based on factors including the available postmarketing experience; extension of use to new patient populations; vaccine uptake; and changes in dosage or formulations that present new safety concerns. In addition, as the epidemiology of mpox continues to evolve, having flexibility for reporting intervals will allow the agency to respond to these changes.

After considering U.S. vaccine uptake of JYNNEOS, which totals more than 1.2 million administered doses as of January 9, 2024[32], available postmarketing safety data, and given that the EUA indication is for use in those at high risk for mpox infection, OBPV supports the proposed LOA amendment to Condition J.

[29] CDC Mpox vaccine administration in the U.S. accessed on August 1, 2024 (As of January 10, 2024, the Centers for Disease Control was no longer updating mpox vaccine administration data.)
[30] U.S. Mpox Case Trends accessed on August 1, 2024
[31] Approval of revised JYNNEOS Package Insert, September 29, 2023
[32] CDC Mpox Vaccine Administration in the U.S. accessed on August 1, 2024

G. Fact Sheet Revisions to Align with JYNNEOS USPI

The following revisions were made to the JYNNEOS Fact Sheets for Health Care Providers Administering Vaccine, to align with the most recent version of USPI

- Revision of 'Monkeypox' to 'mpox', a change made to align with WHO nomenclature. This change was also made to Fact Sheet for Recipients and Caregivers.
- Addition of "facial paralysis (Bell's palsy) under section 6.2 "postmarketing experience". This change was also made to Fact Sheets for Recipients and Caregivers.
- Since the EUA now covers the use of all formulations of commercial products, Section 16.1 was modified to include the following NDCs:
    - Package of 10 single-dose vials
        - Package NDC number: 50632-001-03; Vial NDC number: 50632-001-01
        - Package NDC number: 50632-023-02; Vial NDC number: 50632-023-04
    - Package of 20 single-dose vials
        - Package NDC number: 50632-001-02; Vial NDC number: 50632-001-01
        - Package NDC number: 50632-022-02; Vial NDC number: 50632-022-04

H. Revision of LOA to Remove Requirement that Use of JYNNEOS Under EUA is Limited to Doses Supplied by ASPR

The August 9, 2022, EUA was limited to use of JYNNEOS doses supplied only ASPR from the SNS. Due to changed circumstances, we conclude that this limitation on distribution is no longer necessary or appropriate to protect the public health. Whereas there was previously a need for ASPR to coordinate across federal, state, and local government entities to ensure appropriate allocation of the vaccines and ASPR also maintained all the domestic supply of JYNNEOS, this is no longer the case.

III. RECOMMENDATION

As summarized in the "Disease Background" Section II.A of this memorandum, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the August 9, 2022, declaration by the Secretary of HHS (monkeypox virus) can cause a serious or life-threatening disease or condition.

The global incidence of mpox caused by Clade Ia MPXV and the ongoing outbreak of mpox caused by Clade Ib in Africa with the recent detection of the first Clade Ib mpox case in the U.S. underscore the importance of immunization both globally and in the U.S. The global incidence of mpox is a cause of concern and there continues to be a limited supply of JYNNEOS available globally and in the U.S. and millions of individuals are currently estimated to be at increased risk of mpox in the U.S. and may need vaccination. Another vaccine (ACAM 2000) is approved for use in prevention of mpox disease in the population necessitating emergency uses. However, there are serious adverse reactions associated with that vaccine (as evidence by a boxed warning on its labeling). These adverse reactions include myocarditis and pericarditis, encephalitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, and erythema multiforme major. These risks, including risks of severe disability and/or death, are increased in individuals with cardiac disease; eye disease treated with topical steroids; congenital or acquired immune deficiency disorders. history or presence of eczema and other skin conditions; in infants < 12 months of age; and individuals who are pregnant. In addition, ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those stated for vaccinated individuals. Because of these risks, the use of ACAM2000 may not be appropriate for all individuals determined to be at high risk for mpox infection, especially individuals for whom the

risks are increased. (For more information about the ACAM2000 adverse reactions, see ACAM 2000 USPI for further details.). In addition, because JYNNEOS is a medical countermeasure also approved for the prevention of smallpox, there continues to be a need to maintain a sufficient stockpile supply of both JYNNEOS and ACAM2000 for readiness in the event of a national smallpox emergency. FDA understands that ASPR intends to maintain JYNNEOS and ACAM2000 stockpiles for this purpose. Further, at the time of the 2022 mpox outbreak when there was a severe shortfall in availability for JYNNEOS, the dose-sparing route of administration was an important strategy in ensuring widespread protection. Continued need to consider supply and demand considerations cause FDA to conclude that there is insufficient available approved vaccine for the prevention of mpox. For all these reasons, there is no adequate, approved, and available alternative to the emergency uses of JYNNEOS to prevent mpox.

Based on the available information from several observational studies described in Section II.D, it is reasonable to expect that two doses (each 0.1 mL) of JYNNEOS administered 4 weeks apart by the ID route to individuals 18 years of age and older determined to be at high risk for mpox infection, continues to provide protection against mpox.

Considering the data supporting the licensure of JYNNEOS together with the data described in this review memorandum, the benefits and risks for the ID route of administration still continue to be favorable in individuals 18 years of age and older who are determined to be at high risk of mpox infection. In addition, in the current setting of an outbreak that is continuing to spread in the context of a limited number of vaccine doses, the additional doses of vaccine that can be made available may help to benefit public health measurably by assisting in response efforts.

In addition to the ID route of administration for adults, JYNNEOS administered by the SC route to individuals under 18 years of age determined to be at high risk for mpox infection is reasonable based on the available data in adults vaccinated with JYNNEOS, other live vaccinia virus smallpox vaccines that were used historically in pediatric, and the recent experience with the individual patient IND requests for use of JYNNEOS in pediatric individuals.

Based on the totality of evidence available, the review team concludes that the known and potential benefits of administering two doses (0.1 mL each) of JYNNEOS 4 weeks apart by the ID route of administration to individuals 18 years of age and older determined to be at high risk for mpox infection for prevention of mpox disease, continues to outweigh the known and potential risks for those individuals. Additionally, based on the totality of evidence available, the review team also concludes that the known and potential benefits of administering two doses (0.5 mL each) of JYNNEOS 4 weeks apart by the SC route of administration to individuals younger than 18 years of age determined to be at high risk for mpox infection for prevention of mpox disease, continues to outweigh the known and potential risks for those individuals. Furthermore, based on the review of postmarketing reports, mpox case trends, and vaccine administration trends, OBPV has determined that having flexibility to modify the reporting interval of PSRs would be of value. In addition, it is appropriate to remove the requirement that under the emergency use authorization JYNNEOS must be supplied by ASPR.

Taken together, the review team recommends: 1) removing the requirement that under the emergency use authorization JYNNEOS must be supplied by ASPR; 2) authorizing the continued use of: (a) two doses (0.1 mL each) of JYNNEOS 4 weeks apart by an ID route of administration for prevention of mpox disease in individuals 18 years of age and older determined to be at high risk for mpox infection; and (b) two doses (0.5 mL each) of JYNNEOS 4 weeks apart by a SC route of administration for prevention of mpox disease in individuals younger than 18 years of age determined to be at high risk for mpox infection; 3) revising the Fact Sheets to align with the U.S. Package Insert and 4) revising Condition J of the letter of authorization (LOA) to provide flexibility to determine a different reporting interval for periodic safety reports.