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August 12, 2022

Dear Dr. Chaplin:

This is in response to your letter of August 9, 2022, regarding FDA's emergency use authorization (EUA) for JYNNEOS (Modified Vaccinia Ankara-Bavaria Nordic, MVA-BN) to allow healthcare providers to use the vaccine by intradermal injection for individuals 18 years of age and older who are determined to be at high risk for monkeypox infection. This authorization also allows for use of the vaccine in individuals younger than 18 years of age determined to be at high risk of monkeypox infection; in these individuals JYNNEOS is administered by subcutaneous injection.

One of FDA's top priorities is to address the monkeypox public health emergency as quickly as possible. In recent weeks, the monkeypox virus has continued to spread at a rapid rate that has made it clear our current vaccine supply will not meet the current demand. As of August 11, 2022, there have been 10,768 confirmed cases of monkeypox in the United States. The continued spread of monkeypox has necessitated that FDA vigorously explore all available vaccine options to provide protection for the population at risk..

As you are aware, the supply of JYNNEOS available for distribution through the end of this year is estimated to only be sufficient to immunize half of the individuals at highest risk for monkeypox. In the absence of an adequate supply, we have evaluated the use of alternative vaccines and potential ways to maximize the number of individuals immunized with the available vaccine supply. Use of alternative vaccines was determined to be either impractical or inadvisable at this time.

More specifically, ACAM2000 may not be appropriate now for a potentially immunocompromised population. The local and systemic toxicities of this vaccine may not be considered to be acceptable for the prevention of monkeypox. Consideration was also given to delaying second vaccine doses by 3 to 6 months. However, following careful review of the available animal data with JYNNEOS, and acknowledging the absence of data applicable to this situation, this option was determined to be inadvisable, particularly because it might both be insufficiently protective while at the same time providing individuals with a false sense of reassurance that they were protected against monkeypox when the actual level of protection would be unknown and quite possibly inadequate.

The other options examined looked at approaches that could potentially more effectively provoke an immune response, such as intradermal administration. As you are aware, Stickl and colleagues deployed a Modified Vaccinia Ankara (MVA) in Germany by the intradermal route, treating both children and adults (Stickl HA, Preventive Medicine, 1974; 3:97-101, among others) Since that time intradermal MVA or modified MVA have been used intradermally in several small studies performed in both immunocompetent and immunocompromised individuals (including those with human immunodeficiency virus, HIV).

As you were a co-author (Frey et al, Vaccine, 2015; 33:5225-5234), you are also aware that the MVA vaccine was evaluated as a two-dose series given intradermally compared to subcutaneously in a study sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Individuals who received

the vaccine intradermally received a lower volume (one fifth) than individuals who received the vaccine subcutaneously. The results of this study demonstrated that intradermal administration produced a very similar immune response to subcutaneous (SC) administration. Administration by the intradermal (ID) route did result in more redness, firmness, itchiness and swelling at the injection site, but less pain, and these side effects were manageable. Of note, the side effect profile reported with intradermal administration if JYNNEOS in the NIAID study closely mirrored the side effect profile described initially by Stickl and colleagues (redness and occasional nodularity at the injection).

Based on a careful review of the clinical study report from the NIAID trial and the totality of available evidence in the literature, and considering all available options, FDA determined that the known and potential benefits of the use of intradermal JYNNEOS outweighed the known and potential risks for individuals determined to be at high risk of infection from monkeypox. FDA sought input from others from across academia and the US government and considered all available information prior to making this decision. We refer you to FDA's posted Decision Memorandum for additional information on the authorization.

In your letter, you posed several questions regarding ID administration of JYNNEOS under the EUA. Your questions are copied below followed by FDA's responses:

How long do we have to use the 5 doses per vial?

We understand this question to be how much time can elapse between withdrawing the first dose until administering the 5th dose in each vial. After the vial is punctured and a dose is withdrawn, if it is not used in its entirety, it should be stored at +2°C to +8°C (+36°F to +46°F) and discarded within 8 hours of the first puncture. The FDA's decision is based on stability data submitted by Bavarian Nordic to the approved JYNNEOS Biologics License Application (BLA) and its extensive experience with similar biologic products.

Is 0.1mL appropriate for both PrEP and PEP?

Yes, this dose is appropriate for individuals who are taking PrEP or PEP. The Fact Sheet for Healthcare Providers Administering Vaccine notes that Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to JYNNEOS.

What gauge needle should be used?

A 27-gauge needle should be used as is typically used for intradermal injection. CDC has posted instructions for intradermal administration of JYNNEOS on its website.

How to handle misadministration?

CDC has posted clinical considerations on the website that outline how healthcare providers should handle dosing or administration errors, including how to handle if the vaccine is given in the wrong site, route, dose, or interval. We refer you to CDC's website for information and reporting.

In summary, we certainly appreciate your concerns regarding the potential for reactogenicity associated with ID administration of JYNNEOS. The agency's authorization of the vaccine for emergency use by the intradermal route took this into consideration as part of our evaluation. However, the agency has made its determination with confidence that the safety and efficacy profile of the vaccine will be maintained. Use of

the intradermal regimen will allow us to increase the number of available doses by up to five-fold, allowing more individuals who want to be vaccinated against monkeypox to receive the vaccine to address the current outbreak in the United States. The additional doses provided by using this route of administration will allow us to address the increasing rate of spread of the virus in the United States while providing protection to a broader population.

Thank you for contacting us with your concerns.

Sincerely,

Robert Califf, MD
Commissioner of Food and Drugs

Peter Marks, MD, PhD
Director, Center for Biologics Evaluation and Research