



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

Through: Peter Marks, Director, Center for Biologics Evaluation and Research

To: BLA STN 125682/0

Date: April 30, 2019

Subject: Request from Sanofi Pasteur that FDA designate a nonproprietary name for Dengue Tetravalent Vaccine, Live (DENGVAIXIA) that does not include a distinguishing suffix

Introduction: Sanofi Pasteur has submitted a Biologics License Application for Dengue Tetravalent Vaccine, Live (STN 125682, Action Due May 1, 2019). The proposed indication and usage statement from the draft package insert is as follows: ... the prevention of dengue disease caused by serotypes 1, 2, 3 and 4... for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in dengue endemic areas.

In a July 30, 2018, communication CBER requested that Sanofi Pasteur include a four-letter suffix in the nonproprietary name for Dengue Tetravalent Vaccine, Live, as described in the January 2017 Guidance for Industry: Nonproprietary Naming of Biological Products.¹ The Naming Guidance recommends inclusion of a unique distinguishing suffix for biological products to facilitate pharmacovigilance “when other means to track a specific dispensed product are not readily accessible” and to “help facilitate accurate identification of these biological products by health care practitioners and patients.” Sanofi Pasteur have submitted a number of requests asking the agency to reconsider the request to include a four-letter suffix on the nonproprietary name for this vaccine (email to the BLA chair dated August 6, 2018, a letter to Dr. Marks dated September 13, 2018, and an amendment to the BLA dated February 11, 2019).

Sanofi Pasteur’s amendment (February 14, 2019, Appendix A) states “we believe that the application of [the 2017 Guidance for Industry Non-proprietary Naming of Biological Products] should not apply to our submission as it would not advance the principles articulated therein. In fact we are concerned that it will be difficult to practically implement and ultimately may create confusion amongst health care providers within the immunization community, and thus not advance the collective public health interest to increase immunization rates here in the US.” Additionally, Sanofi notes that “imposition of random suffixes to a vaccine label could be confusing and create negative public health impacts.” This memorandum addresses Sanofi Pasteur’s request and documents the justification for and my

¹ Guidance for Industry, Nonproprietary Naming of Biological Products (Jan. 2017) (hereinafter Naming Guidance), available at <https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf>.

supervisory concurrence with the decision to depart from the recommendations in the Naming Guidance in approving a non-proprietary name without a suffix for this product.²

Summary:

After reviewing the request from Sanofi Pasteur, and considering the relevant facts at hand, I have concluded that the existing mechanisms to track this product are sufficient to ensure safety and pharmacovigilance and a suffix on the nonproprietary name is not necessary for the safe use of this vaccine and may have unintended consequences as described below.³

The issue of whether to designate the nonproprietary name of this vaccine without a distinguishing suffix was discussed with the FDA Biosimilar Implementation Committee on April 10, 2019.⁴ The committee, including Dr. Marks and Dr. Woodcock, agreed with OVRP that a distinguishing suffix was not needed in this case and further recommended that if we designate a proper name without a distinguishing suffix for this vaccine, we should document this departure from the Naming Guidance. As Director of OVRP, I am the supervisor to OVRP staff who reviewed this BLA. This memo documents my concurrence with the decision to depart from the Naming Guidance.

Consideration of the request from Sanofi Pasteur regarding Dengvaxia:

The fundamental question is whether the inclusion of the suffix in the proper name for Dengvaxia is necessary for safe use, or whether other measures are in place that are sufficient to ensure safe use and pharmacovigilance.

This memo describes unique vaccine administration recording requirements and safety monitoring programs for vaccines, including requirements for vaccines subject to the National Vaccine Compensation Injury Program. The totality of circumstances associated with the administration of vaccines, including the unique recordkeeping requirements, monitoring systems, and public health considerations, supports the review team recommendation and my decision to depart from the Naming Guidance and to designate a proper name without a distinguishing suffix for this vaccine.

1. Vaccination Records

Unique recordkeeping requirements associated with the administration of vaccines, including those associated with the National Childhood Vaccine Injury Act and Immunization Information Systems,

² See 21 C.F.R. § 10.115(d)(3) (“Although guidance documents do not legally bind FDA, they represent the agency’s current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.”).

³ Sanofi Pasteur made additional arguments in support of its February 11, 2019 request. However, because the Agency found it appropriate to agree with Sanofi on the grounds described in this memorandum, we do not consider or address those additional arguments.

⁴ The CDER/CBER Biosimilars Implementation Committee is a cross-center workgroup within FDA, including Dr. Janet Woodcock and Dr. Peter Marks, that discusses issues regarding the implementation of the BPCI Act.

provide for the identification of most vaccines by their manufacturer (and potentially by lot number), without the need for a distinguishable suffix.

National Childhood Vaccine Injury Act: Most US-licensed vaccines are subject to The National Childhood Vaccine Injury Act of 1986. Covered vaccines are those recommended for routine administration to children or pregnant women by the CDC, subject to an excise tax by federal law and added to the Vaccine Injury Compensation Table by the Secretary for HHS.⁵

For vaccines included in the “Vaccine Injury Table” (which include most of the US-licensed vaccines) there are additional recordkeeping requirements that permit the identification of the vaccine administered without a suffix. For those vaccines included in the “Vaccine Injury Table” the National Childhood Vaccine Injury Act of 1986 requires each healthcare provider (HCP) who administers a vaccine included in the “Vaccine Injury Table” to record in the vaccinee’s permanent medical record 1) the date of administration of the vaccine, 2) the vaccine manufacturer and lot number, and 3) the name and address and, if appropriate the title of the HCP administering the vaccine.⁶ This requirement is unique for vaccines. This Act applies to any vaccine for which there is a routine recommendation for childhood vaccination, even if many or most doses of the vaccine are administered to adults (e.g., influenza vaccine).

For those vaccines that are not included on the Vaccine Injury Table, the Advisory Committee on Immunization Practices recommends that “This information should be kept for all vaccines, not just for those required by the Act.” (<https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/records.html>). Therefore, it is reasonable to expect that many healthcare providers would maintain this information, and use similar recording systems, for all vaccines administered, not just those included in the Vaccine Injury Table, and that information to allow identification of a vaccine’s manufacturer would be captured routinely for most vaccines.

Immunization Information Systems: Unlike records associated with other drugs or biologics, vaccination records are required for child care, school, summer camps and international travel. These records are retained by the clinic or HCP office in a patient’s chart. To facilitate retrieval of records, almost all states have an Immunization Information System (IIS) (New Hampshire does not have an IIS). IIS are centralized population-based repositories of immunization related information. They receive and share data on individual clients/patients with a number of other systems, including Electronic Health Record systems (EHR-S). One of the goals of the IIS is to promote vaccine safety in public and private

⁵ Covered vaccines: Diphtheria, Tetanus, Pertussis, Haemophilus influenzae type b, Hepatitis A, Hepatitis B, Human papillomavirus, Seasonal Influenza, Measles, Mumps, and Rubella, Meningococcal, Pneumococcal conjugate, Polio, Rotavirus, and Varicella, in any combination. The following approved vaccines are not covered: adenovirus, anthrax, cholera, herpes zoster, non-seasonal influenza, rabies, Japanese Encephalitis, pneumococcal polysaccharide, yellow fever, small pox and typhoid. Although a determination regarding whether DENG VAXIA is a “covered vaccine” for the purpose the NCVA will not be made until after the approval of the vaccine, we do not anticipate that DENG VAXIA will be covered.

⁶ <https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf>

provider settings and enable the identification of vaccine recipients by vaccine lot, manufacturer, provider, and/or time frame – consistent with the NCVIA of 1986 but not limited to vaccines subject to the Act.

Participation in IIS is widespread and supported by the federal government. One of the national Healthy People objectives for 2020 is 95% participation of children aged <6 years in a fully operational population-based IIS (participating in an IIS means having two or more vaccinations recorded in the IIS). IIS data from 2012 indicate that approximately 86% of children aged <6 years with two or more vaccinations were participating in IISs (CDC. Progress in immunization information systems – United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2013;62(49):1005-1008. Mangione-Smith R, DeCristofaro AH, Setodji CM, et al. The quality of ambulatory care delivered to children in the United States. *N Engl J Med.* 2007;357(15):1515-1523. DOI: 10.1056/NEJMsa064637).

Nationally, 57.8 million U.S. adults aged 19 years or older participated in an IIS in 2012 (CDC. Progress in immunization information systems – United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2013;62(49):1005-1008.). This number reflects adults who may have had childhood vaccines entered during childhood and now have aged to adults. In 2013, 32% of U.S. adults had a record in the IIS and at least one vaccination administered during adulthood.

The National Vaccine Advisory Committee (established to comply with Section 2105 of the Public Health Service Act) recommends that public health departments work toward including adults in all state IISs, reduce barriers to including adult vaccination records in IISs, and ensure that IISs meet new standards of EHR interoperability to track and maintain adult vaccination records.

2. Vaccine Safety Monitoring Systems

The Vaccine Adverse Event Reporting System:

VAERS is a national program managed by the FDA and CDC to monitor the safety of all vaccines licensed for use in the US. FDA and CDC conduct safety surveillance for vaccine-associated safety concerns utilizing VAERS. This system is valuable for signal detection, and it has unique characteristics that differentiate it from other adverse event surveillance systems. As a preliminary matter, in addition to mandatory reporting of adverse events by manufacturers that is common to all drugs and biologics, for vaccines covered by the National Childhood Vaccine Injury Act, there is mandatory reporting for healthcare providers for any event listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine and any adverse event found in the “Reportable Events table” that occurs within the specified time after vaccination.

The form that is used for VAERS, which mirrors the information required to be collected under the NCVIA, further permits the accurate identification of the event and the vaccine administered. VAERS requires the vaccine name (“type and brand name”), manufacturer, and lot number. The form permits the user to enter the vaccine type/brand name manually or to select a specific vaccine identified by abbreviation/disease and proprietary name from a “pick list.” ([https://vaers.hhs.gov/docs/VAERS Table of Reportable Events Following Vaccination.pdf](https://vaers.hhs.gov/docs/VAERS%20Table%20of%20Reportable%20Events%20Following%20Vaccination.pdf)). While it may be possible for the FAERS system that covers other biologics and drugs to adopt a similar format, at

this time, this format is unique to VAERS and is permitted, in part, because of the limited scope of products covered by the reporting system.

The Vaccine Safety Datalink: The Vaccine Safety Datalink (VSD) project is a collaboration between the National Immunization Program of the CDC and several HMOs. The project began in 1990 with the purpose of rigorously evaluating concerns about the safety of vaccines. According to the CDC, the VSD generates rapid, important safety assessments for both routine vaccinations and emergency vaccination campaigns.⁷ To accomplish this, the VSD uses electronic health data from each participating site that includes information on vaccine type, vaccine manufacturer, vaccine lot number, date of vaccination, and other vaccinations given on the same day. Participating healthcare organizations cover more than 9.1 million people nationwide (over 3% of the US population).

3. Additional considerations for vaccines:

As noted by Sanofi Pasteur the four-letter suffix will likely be interpreted by some in the public to refer to an unintended and non-specific attribute to the product. Some individuals may believe this refers to an unidentified ingredient, a new adjuvant or an abbreviation for a chemical. This may cause confusion and concern regarding the safety of the vaccine. This confusion is particularly concerning given increased public concerns about the safety of vaccination and rising levels of refusals to vaccinate. Decreased confidence in vaccine safety does not just affect the health of patients who refuse to vaccinate, as is the case with decreased confidence in therapeutic biologic products. Confusion surrounding vaccine safety could undermine the effectiveness of the vaccine program overall and, ultimately, lead to negative public health effects, including outbreaks of preventable diseases.

Attachment:

Appendix A: February 14, 2019, amendment to STN 125682/0.25 (Sequence 0023) from Sanofi Pasteur



STN 125682 -
Dengvaxia - Suffix Req

⁷ Vaccine 32 (2014) 5390–5398