

From: Polo, Stephanie
Sent: Friday, April 19, 2019 3:35 PM
To: Patrick.O'Neil@sanofi.com
Cc: Prutzman, Kirk C <Kirk.Prutzman@fda.hhs.gov>; Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>
Subject: STN 125682-Information Request

Dear Mr. O'Neil,

We have the following request for additional information regarding STN 125682 (Dengue Tetravalent Vaccine, Live):

The following comments pertain to the minimum release specification:

1. We do not agree that the data support a lower limit release potency specification of (b) (4) \log_{10} CCID₅₀. The data you submitted in your original submission and in Amendments 22 and 30, based on assay variability and product stability, indicates a need to set the minimum release specification of Dengvaxia at (b) (4) \log_{10} CCID₅₀ above the potency considered to be efficacious (expiry potency) to ensure that lots will meet expiry potency at the end of the shelf life with 95% confidence. The immunogenicity data from CYD12 does not confirm that a (b) (4) dose of Dengvaxia is comparable to a "5/5/5/5" dose of Dengvaxia. Therefore, at the current release specification, it is possible that an individual may receive a dose of Dengvaxia where the potency of one or more CYD Virus serotypes is below (b) (4) \log_{10} CCID₅₀. Please revise your lower limit release potency specification from (b) (4) \log_{10} CCID₅₀ to (b) (4) \log_{10} CCID₅₀. Please update your lot release protocol and all the documents in the BLA that contain the lower limit release potency specification to include the new (b) (4) \log_{10} CCID₅₀ specification.

The following comment pertains to the stability of the reconstituted vaccine:

2. In the package insert, you indicate that the reconstituted vaccine can be stored at 2°C-8°C for up to (b) (4) before administration. Based on the data you present (3.2.P.8.3, Tables 11, 12, and 13), our calculations indicate potency loss after reconstitution when stored at 2°C-8°C. Please reduce the time that the reconstituted vaccine can be stored at 2°C-8°C after reconstitution from (b) (4) to 30 minutes.

The following comments pertain to the diluent (0.4% NaCl):

3. Please specify the target volume (or fill (b) (4)) for the diluent filled into 2 mL final containers.
4. We note that the in-process control acceptance criteria for diluent Fill (b) (4) is (b) (4) (3.2.P.3.4). We are concerned that these wide acceptance criteria could result in lack of dose consistency. In Table 4 (3.2.P.3.4), it is indicated that "...The upper limit...has no impact on the potency of the vaccine as the recommended amount of diluent is removed from the vial for reconstitution of the lyophilized vaccine." However, this justification is not consistent with the instructions for dose preparation for administration in the package insert (2.2 Preparation), where it is indicated to "withdraw the entire content of the diluent vial and inject it into the vial of the lyophilized vaccine." Please tighten the acceptance criteria for Fill (b) (4) to ensure consistent dosing or justify the current specification.

5. The acceptance limit for Vial Volume for Final Container Diluent Drug Product (Unlabeled) is (b) (4) (3.2.P.5.1). Please include an upper limit or provide a justification.

Please submit your response as an amendment to STN 125682 by Tuesday, April 23, 2019.

If you have any questions, please contact Kirk Prutzman, Stephanie Polo or Ramachandra Naik at (301) 796-2640.

Best regards,

Stephanie Polo

Primary Reviewer/Regulatory Project Manager

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