

From: Polo, Stephanie
Sent: Friday, March 15, 2019 5:31 PM
To: 'Patrick.O'Neil@sanofi.com' <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, Attenuated]):

1. Regarding the qualification of the cell banking system, we note that (b) (4) adventitious agents were conducted on the (b) (4) and (b) (4). Please clarify whether future (b) (4) will be qualified in the same manner as described in the BLA at (b) (4). Please consider submitting a comparability protocol for the qualification of future (b) (4).
2. The following comments pertain to the qualification of the working seed lots (WSLs) and master seed lots (MSLs):
 - a. Please provide the lot number, date of production and certificate of analysis (COA) for the (b) (4) MSLs, MSLs, and WSLs lots used for production of Phase 3 lots and process performance qualification (PPQ) lots. Please provide this information in a table reflecting of the genealogy of the seed lots and specifying which WSLs will be used for commercial vaccine production.
 - b. Please consider submitting a comparability protocol for the use of future WSLs and consider including the following additional assessments for the qualification of the WSLs:
 - (b) (4)
 - (b) (4) based on 9 CFR 113.53 requirements
3. The container closure system for CYD dengue drug substances (DS) is a (b) (4). Please provide the name of the manufacturer, specifications and material of construction of the (b) (4).
4. Regarding the (b) (4) used for cell culture, please provide the name of the manufacturer, specifications and material of construction, and analysis of extractable studies.
5. Regarding manufacturing equipment information, for the (b) (4) chromatography ((b) (4)), ultrafiltration (b) (4) and the 0.2 µm filtration system used for the DS and drug product (DP), please provide a description of the equipment and construction materials that come into contact with the product and name of manufacturer. In addition, please provide the number of allowed reuses, qualification information to support reuse (if applicable), and storage duration and condition between reuses.
6. Please include the (b) (4) used in the (b) (4) in section 3.2.S.5 and 3.2.P.6 (Reference Standards or Materials).

7. The DS lots may be stored for up to (b) (4). We note that Table 4 in Section 3.2.P.3.5 *Process Validation and Evaluation* includes DP lots manufactured with DS lots stored for approximately 36 months. To support the proposed shelf life of the DS lots, if available, please provide DP release and/or stability data for lots produced with DS lots stored for close to (b) (4).
8. The Final Bulk Product is formulated at (b) (4)
(b) (4)
(b) (4) Please clarify if the (b) (4) target was applied to the Phase 3 and PPQ lots submitted to the BLA and comment or provide an assessment of the overall potency loss during the DP manufacturing steps.
9. We note that the stabilizing solution (containing essential and non-essential amino acids, hydrochloric acid, L-arginine hydrochloride, sucrose, D-trehalose dehydrate, D-sorbitol, trometamol, urea, and sodium chloride) added during the formulation of the final bulk product (FBP) does not undergo any testing prior to use and none of the stabilizing components are tested in the final bulk product (FBP). The following comments pertain to the stabilizing solution used for formulation of the FBP:
- Please include a description of the manufacturing controls applied to the formulation of the stabilizing solution (such as those described in the briefing package submitted to IND 11219 on May 1, 2019) in section 3.2.P.3.3 under the section 1.2.1 Preparation of the FBP Stabilizing Solution.
 - Please detail what quality control tests are done on the stabilizing solution. Please include this information in section 3.2.P.3.3 as specified above and in section 3.2.P.4.1 Specifications (for Excipients).
 - The stabilizing solution is stored at (b) (4); however, no information was provided regarding the shelf life of the solution and the container closure system used for storage.
 - Please provide the expiry date for this solution and stability data to support the proposed expiry.
 - Please provide a description of the container closure system used for storage, as well as material of construction, name of manufacturer, and leachables and extractables information.
 - Please specify which components are considered stabilizing agents (i.e., having activity beyond buffering) and how these will be tested in the final product.

Please submit your response in an amendment to STN 125682 by Monday, April 1, 2019. We recommend that you restate each item and follow it with your explanation or clarification. Use of this format helps to organize the relevant information and provides a self-contained document that facilitates future reference. If you have any questions, please contact Kirk Prutzman, Stephanie Polo or Ramachandra Naik at 301-796-2460.

Best regards,

Stephanie Polo

Primary Reviewer/Regulatory Project Manager

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