

From: Polo, Stephanie
Sent: Friday, March 01, 2019 4:05 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. In your justification of specifications (Section 3.2.P.5.6), we note your statement (about study CYD12) that “The virus concentration of this batch formulated at (b) (4) ranges from (b) (4) \log_{10} CCID₅₀/dose at the time of injection with a mean value for the 4 serotypes at (b) (4) \log_{10} CCID₅₀/dose.” Please provide all data that support this conclusion, considering the starting potency of lots used in CYD12 exceeded your proposed release potency of (b) (4) \log_{10} CCID₅₀/dose for three of the four serotypes (Appendix 14 of CYD12 CSR). To the extent that this calculation includes data other than product stability data at the requested storage temperature (at which you have indicated that the product is highly stable), please explain how these data differentially affect lots employed in study CYD12 vs. lots that might be considered for release, post-licensure.
2. We note the conclusions from study CYD12, which state, in part:
 - In general, the lowest seropositivity rates, except for serotype 4, were observed in Group 3.
 - The percentage of subjects seropositive to all 4 serotypes was highest in Group 1 after each vaccination; therefore, providing the most balanced antibody immune response to the 4 dengue virus parental serotypes.
 - In general, the lowest GMTs for all serotypes, except for serotype 4, were observed in Group 3.

Given your own conclusion that subjects who received the (b) (4) lots in Group 3 generally had lower immune responses than those receiving 5/5/5/5 lots in Group 1, please provide a cogent rationale for the relevance of study CYD12 to determining the appropriate end-expiry potency for Dengvaxia serotypes 1-3.

3. Given the uncertain relevance of study CYD12 to determining the appropriate end-expiry potency for Dengvaxia serotypes 1-3 (except, apparently, to indicate an unacceptable level), please present any additional data that might support end-expiry potency at levels below those tested in studies CYD14 and CYD15.
4. In your response to our 1/11/19 information request, Question 1 (Amendment 22), you refer to stability studies on (b) (4) additional lots, comprising two additional ICH stability studies (with (b) (4) lots each) and two ongoing stability studies that were not included in the original BLA submission. You indicate significant and substantial decay of serotype 1 potency in these studies, but state that these studies demonstrate stability of the other three serotypes because the slopes were not significantly different from zero. We note that a failure to demonstrate a decay slope significantly different from zero does not

prove that a product is stable through the dating period. For example, an underpowered study and/or high variability in the potency assay could also contribute to this outcome. Please present the raw data from these stability studies and your calculations to justify the conclusions you make in Amendment 22.

5. Typically, vaccine release potencies are set to exceed end-expiry potencies in a way that the batch will remain within the expiry acceptance criterion throughout the shelf life with 95% confidence, taking into account release assay variability, potency loss due to stability, and precision of stability estimates (e.g., as discussed in the 2006 WHO "Guidelines on Stability Evaluation of Vaccines" and further described in Biologicals. 2009 Nov;37(6):369-78). We note that your proposed release potencies do not formally account for any of these factors. Please present a formal analysis that justifies your release potencies for each serotype, considering these factors and the clinical data that you believe supports your proposed release potencies.
6. You request a (b) (4) specification from (b) (4), based on an analysis of manufacturing variability. Normally, the (b) (4) specification is chosen to assure that the product will be released at a (b) (4) that assures stability throughout the dating period. The (b) (4) lots presented in the stability study were all released at a (b) (4) with a range on stability study of (b) (4). The three consistency lots in CYD17 were released at (b) (4), and (b) (4). The clinical lots (CYD14 and CYD15) were released at (b) (4), respectively. Please present a justification for your (b) (4) specification that relies on product attributes demonstrated to be associated with desired characteristics, rather than one that simply relies on an analysis of manufacturing variability.

Please submit your response in an amendment to STN 125682 by Monday, March 18, 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

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