

From: Prutzman, Kirk C
Sent: Tuesday, February 26, 2019 5:31 PM
To: Patrick.O'Neil@sanofi.com
Cc: Polo, Stephanie <Stephanie.Polo@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 your "Request for a Waiver of Pediatric Studies" (eCTD Section 1.9.1) for infants 0 to <2 years of age included in STN 125682 (Dengue Tetravalent Vaccine [Live, Attenuated]):

In your partial waiver request, you have indicated three reasons for CBER to grant a waiver of the requirement to submit an assessment in infants 0 to <2 years of age. They are:

- The CYD dengue vaccine may be unsafe in individuals <2 years classified as dengue-seropositive
- The CYD vaccine may be ineffective in seropositive individuals <2 years classified as dengue-seropositive
- The CYD vaccine is not likely to be used in a substantial number of pediatric individuals below 2 years of age

As stated, your partial waiver request cites but does not fully address two of the statutory criteria listed in the Pediatric Research Equity Act. They are:

1. There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).
2. The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

For each age group for which you are requesting a partial waiver, please provide a justification for the chosen criterion. Please note, if you choose criterion 1 above, you must describe the evidence that strongly suggests Dengvaxia is ineffective or unsafe in the referenced age group, and you must also include this information in the Prescribing Information (PI). This information is generally included in the *Pediatric Use* subsection of labeling. Currently, your proposed PI does not include this information. If you choose criterion 2 above, you must provide a justification that both explains why Dengvaxia does

not represent a meaningful therapeutic benefit over existing therapies for the referenced age group and explains why Dengvaxia is not likely to be used by a substantial number of children in that age group. Currently your request for a partial waiver does not include a justification explaining why Dengvaxia does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in infants 0 to <2 years.

You may request a single partial waiver for the age group birth to <2 years, if justified by a single statutory criterion, or you may request more than one partial waiver (e.g., one request for the age group birth to <1 year and one request for the age group 1 to <2 years) if the requests are justified by different statutory criteria. In considering your justification for a partial waiver of the pediatric assessment in the age group birth to <2 years, we think it is important to discuss the impact of maternal antibodies on laboratory confirmation of dengue infection separately for younger and older infants in this age range.

You should request a deferral for any age group for which available data are not sufficient to justify a partial waiver request and for which you have not already submitted a pediatric assessment. Thus, if based on our above requests for information, you decide to limit your request for a partial waiver to only a subset of the age group birth to <2 years of age, then your deferral request would need to be revised. For example, while Dengvaxia may not provide meaningful benefit over maternal antibodies in younger infants, we do not expect that maternal antibodies will persist in older infants, who may then experience dengue infection amenable to laboratory confirmation prior to 2 years of age. Consequently, Dengvaxia may provide meaningful benefit for older infants <2 years of age with laboratory confirmed previous dengue infection and living in endemic areas, and currently available evidence may not strongly suggest that Dengvaxia is unsafe in this population. Any deferral request should state the reasons for the deferral based on available data and state your plan for completing the pediatric assessment for that age group. You should provide a description of planned and on-going studies; evidence that planned or on-going studies are proceeding; and a projected date for submission of the pediatric assessment for this age group.

Please submit a revised "Request for Waiver of Pediatric Studies" that addresses the above comments.

Please submit your response by March 04, 2019. You may respond by email for expediency and then submit your response in an amendment to STN 125682 at a later date. 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.

Regards,

Kirk Prutzman, PhD

Primary Reviewer/Regulatory Project Manager

CBER/OVRR/DVRPA/CMC3

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