

RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125682/0
Review Office	OVR
Applicant	Sanofi Pasteur, Inc. / Lic. # 1725
Product	Dengue Tetravalent Vaccine, Live

Telecon Details

Telecon Date/Time	March 1, 2019, 01:00 PM
Author	NAIK, RAMACHANDRA
FDA Originated?	Yes
Communication Categories	IR - Information Request
Telecon Summary	Discussion regarding Sanofi's pediatric waiver request
FDA Participants	Sarah Browne Karen Farizo Doran Fink Ralph LeBlanc Lucia Lee Ramachandra Naik Stephanie Polo Kirk Prutzman Elizabeth Sutkowski
Applicant Participants	Patrick O'Neil Gustavo Dayan Francois Verdier Elise Lefebvre

Background:

In an email dated February 26, 2019, CBER requested additional information regarding Sanofi's request for a partial waiver of pediatric studies and asked Sanofi to submit a revised "Request for Waiver of Pediatric Studies" that addresses the comments included in the IR (see Attachment 1). Sanofi requested a teleconference to discuss the pediatric waiver issues, and provided via email on February 28, 2019, clarification questions to be discussed (see Attachment 2). The telecon with Sanofi was held on March 1, 2019.

Summary of Discussion:

Regarding the February 28, 2019 email from Sanofi, CBER informed Sanofi that they would need to provide revised waiver and deferral requests that reflect their new plans to provide assessments in children <9 years. CBER noted that any proposal must contain an appropriate justification and data to support their justification. Sanofi indicated that they can provide an appropriate justification.

CBER discussed that if Sanofi has strong evidence that Dengvaxia is unsafe or not effective in individuals <2 years, they would need to include language in the package insert that reflects the waiver request. CBER discussed that maternal antibodies should not interfere with safe

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administration of Dengvaxia. CBER agreed that maternal antibodies might lead to a false positive test result, but expressed doubt that maternal antibodies persist up to 2 years of age.

CBER informed Sanofi that if they choose option 2 (Attachment 2), their request for a waiver should satisfy both parts – the drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies and (2) is not likely to be used by a substantial number of pediatric patients in that age group.

CBER discussed that if Sanofi does not have sufficient data to support a waiver for the age group of <2 years, they can propose to request a waiver for age group (e.g., <6 months, due to the presence of maternal antibodies) and deferral for the remaining age groups not covered by the BLA (e.g., 6 months – 8 years). Sanofi stated that they will analyze the data and submit the revised waiver and deferral requests.

Sanofi asked if they could submit the revised documents by March 18, 2019, and CBER agreed that would be acceptable. However, CBER asked Sanofi to send them by email for expediency, followed by an official amendment submission to the BLA. Sanofi agreed.

Call ended.

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Attachment 1:

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*

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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.

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Regards,

Kirk Prutzman, PhD

Primary Reviewer/Regulatory Project Manager

CBER/OVRR/DVRPA/CMC3

Food and Drug Administration

10903 New Hampshire Avenue

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Silver Spring, MD 20993-0002

Phone: (301) 796-2640

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Attachment 2

From: Patrick.O'Neil@sanofi.com <Patrick.O'Neil@sanofi.com>
Sent: Thursday, February 28, 2019 7:38 PM
To: Prutzman, Kirk C <Kirk.Prutzman@fda.hhs.gov>
Cc: Polo, Stephanie <Stephanie.Polo@fda.hhs.gov>; Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>
Subject: RE: STN 125682 - Information Request

Hi Kirk – Sure.

We wanted to confirm our understanding of the statute was correct. I believe you broke it down in to two options:

- Option 1: Vaccine is unsafe **or** ineffective for pediatric patients. If so we must include related information in the labeling
- Option 2: (a): Vaccine is not likely to be used by a substantial number of pediatric patients **and**
(b): Vaccine does not represent a meaningful benefit over existing therapies

CBER Questions

1. We prefer to avoid including unsafe or ineffective language in the label and as a result – prefer Option 2. Subpart (a) could be met since the likelihood of children <1 y contracting dengue is low. Concerning subpart (b) - there may be no true benefit since the maternal antibodies may “mask” a true test result? Do you think your internal Pediatric Review Board would find this acceptable?
2. If we pursue Option 1 by amending the label – is it acceptable to state that the vaccine is potentially ineffective up to 12 months due to the maternal antibody effect or would we need to instead highlight that the resulting impact may be that is potentially unsafe?
3. We would like to modify our deferral so it encompasses 1 – 8 year olds. Can you confirm that this is acceptable?

Any guidance you can provide us to satisfy your Review Board would be greatly appreciated.

Thank You Kirk

Pat