



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 8 April 2019
To:
From: Hong Yang, Ph.D.
Analytics and Benefit-Risk Assessment Team
OBE
Through: Richard Forshee, Ph.D.
Chief, Analytics and Benefit-Risk Assessment Team
OBE
Re: STN 125682/0: review memo for benefit-risk assessment
STN 125682/0.19 (1/18/2019)
STN 125682/0.21 (2/8/2019)

Review Memo on Benefit-Risk Assessment of Dengvaxia

Reference submission: BLA 125682/0, Quantitative Benefit-Risk Analysis (Section 1.11.4 Multiple Module Information Amendment submitted to FDA in March 2019)

Reviewer: Hong Yang

Date: 4/5/2019

I. Dengue Endemic Areas in the U.S. with Co-Circulation of Other Flaviviruses

Proposed indication for Dengvaxia is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through <17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Thus, the use of Dengvaxia is contingent upon a novel “screen-and-vaccinate” approach. Pre-vaccination screening for “*laboratory-confirmed previous dengue infection*” can be assessed in two ways: (i) through a medical record of a previous laboratory-confirmed dengue infection or (ii) through current serotesting. There is concern that the cross-reactivity to other flaviviruses of available serotesting assays may result in higher number of false positives for prior dengue exposure; thus, higher risk of excess cases of severe and/or hospitalized dengue following vaccination in previously unexposed individuals. Therefore, identification of dengue endemic areas in the US with co-circulation of other flaviviruses is important. FDA agrees with Sanofi on this part of assessment.

- a. CDC determined that four U.S. territories Puerto Rico, the U.S. Virgin Islands, American Samoa and Guam, are endemic (frequent/continuous risk) for the dengue virus (<https://www.cdc.gov/dengue/epidemiology/index.html#dengue-surveillance>). Vaccination of Dengvaxia may be recommended in these regions if it is approved. A few small sporadic dengue outbreaks and dengue cases related to travel exposure have been reported in the other regions in the U.S. However, Dengvaxia will not be used in those regions based on its current indication.
- b. There is co-circulation of Zika in Puerto Rico, the U.S. Virgin Islands and American Samoa (<https://wwwnc.cdc.gov/travel/page/zika-travel-information>). There is concern about the higher number of false positives for prior dengue exposure, and increased risk of excess cases of severe and/or hospitalized dengue following vaccination in previously unexposed individuals in these three regions.
- c. Among above three U.S. territories, Puerto Rico has largest population and likely higher Zika sero-prevalence as result of 2016 Zika outbreak. Performance of available serotests has never been tested in Puerto Rico post-Zika outbreak. Applying “Screen-and-vaccinate” in Puerto Rico likely represents the worst-case scenario for the risk of excess severe and/or hospitalized dengue cases due to the result of cross-reactivity to other flavivirus from pre-vaccination screening. For this reason, FDA reviewers agree to focus benefit-risk assessment of Dengvaxia in Puerto Rico.
- d. There is local transmission of West Nile virus in the U.S.; however, there is no co-circulation of dengue virus in those regions.
- e. There is no local transmission of other flaviviruses in the U.S.

II. Benefit-Risk Assessment of Dengvaxia with Screen-and-Vaccinate Approach in Puerto Rico

Sanofi submitted benefit-risk assessment using two different approaches: static and dynamic approaches.

Dynamic Approach by Sanofi:

A dengue transmission model previously published by Sanofi (Laurent et al. *Vaccine* 34, 2016) was used to assess outcomes of dengue disease over 5 –30 years post vaccination. The disease transmission model is complex, and many model parameters are specific to the disease epidemiology of the region. Sanofi developed the model for Puerto Rico using data collected during the CYD15 trial. With limited data/information specifically from Puerto Rico and unknown long-term vaccine efficacy we expect great uncertainty with model outcomes, thus limited utility of the model.

Static Approach by Sanofi:

FDA's review focuses on the static approach. The overall approach seems reasonable. It focuses on the benefit (number of severe dengue cases prevented among the population with prior dengue exposure) and risk (excess severe dengue cases from population without prior exposure to dengue virus but are falsely tested positive by pre-vaccination screening). The scope of the assessment was limited to the benefit-risk within 5-years post vaccination of age group 9-16 years old. The model outcome is informative for its purpose. Most of the model inputs and assumptions appear to be reasonable. FDA used the incidence rate of CDC reported dengue cases as external validation of Sanofi extrapolated incidence rates for Puerto Rico (Table 5, response to Q4 FDA IR for Benefit-Risk). The weighted average of 5-year cumulative severe dengue incidence of placebo seropositive and seronegative groups for Puerto Rico submitted by Sanofi is approximately 1×10^{-3} . The 5-year cumulative dengue incidence in Puerto Rico 2012-2016 reported by CDC was about 5×10^{-3} (Rosenberg et al. MMWR, May 2018). By comparing these two incidence rates we consider Sanofi's extrapolation for dengue incidences for different groups in Puerto Rico reasonable. However, we identified two assumptions used in Sanofi's analysis that may lead to underestimate of excess severe dengue cases from population having no previous exposure to dengue virus:

1. Percentage dengue seronegative among Zika seropositive: 13% used by Sanofi vs 44% proposed by FDA

Sanofi's assumption is based on the data from CYD 15 Immunogenicity Study placebo group which shows 87% of Zika seropositive was also dengue seropositive. The proportion of a population who have exposure to both Zika and dengue viruses depends on the local history and dynamics of these two diseases. FDA reviewers consider it inappropriate to apply the data from other regions to Puerto Rico. Only 6% of participants in CYD 15 were from Puerto Rico. Considering likely high Zika seroprevalence in Puerto Rico due to the 2016 Zika outbreak this extrapolation probably underestimates the size of the population at risk for false positive for prior dengue exposure due to cross-reactivity to Zika.

We assumed 56% of Puerto Rico population is dengue seropositive based on the reference presented by Sanofi. There is insufficient evidence to ascertain that there is a correlation between the exposure to dengue and Zika viruses. For public health protection, we consider it reasonable to apply the same percentage (56%) to the subgroup who are Zika seropositive as a conservative assumption. Therefore, FDA suggests using 44% (56% less 100%) as the input in the analysis for Percentage Dengue Naive among Zika Seropositive.

2. Cross-reactivity of Tell Me Fast Dengue IgG/Ig RDT [Biocan] for the worst-case scenario: 2.6% used by Sanofi vs. 8% proposed by FDA

We assumed the Biocan RDT would be used in Puerto Rico to screen individuals with prior dengue exposure. Sanofi used lower bound of assay sensitivity and specificity in the benefit-risk assessment

to represent the worst-case scenario for assay performance. FDA concurs with Sanofi's approach which is conservative and appropriate for public health protection. Based on the data presented by Sanofi, to assess the cross-reactivity to Zika virus a total of thirty-eight Zika positive/dengue negative samples were tested using Biocan RDT. Among them one sample was tested false positive for prior dengue exposure. The ratio of one out of thirty-eight yields a mean of 2.6% and 95th upper bound of 8% for cross-reactivity to Zika. Sanofi used the 2.6% mean value in the analysis. FDA suggests taking similar conservative approach for assay cross-reactivity for the worst-case scenario by using upper bound value (8%) in the benefit-risk analysis.

Below are additional comments on Sanofi's benefit-risk assessment:

1. Subgroups with and without prior dengue exposure have distinct benefit-risk profiles. Vaccination in seropositive individuals has a favorable benefit/risk profile with protection against hospitalized and severe dengue; whereas vaccination in seronegative individuals was identified with increased risk of hospitalized or severe dengue. Risk transfer from one group to another could be a sensitive issue. Presentation of benefit-risk by two groups separately is important for better understanding the magnitude of risk for the high-risk group and the need for risk mitigation.
2. FDA reviewers consider a benefit-risk assessment for most-likely scenario using mean sensitivity, specificity and cross-reactivity of Biocan RDT in addition to the worst-case scenario may be helpful for better understating the impact of uncertainty associated with assay performance on the benefit-risk assessment.
3. Sensitivity analysis of model inputs for seroprevalence of dengue and Zika among target population is important because they have great impact on both benefit and risk of vaccination. Seroprevalence are changing overtime depending on the dynamics of the diseases and vary by age group.
4. Sensitivity analysis of cross-reactivity of serotest is also helpful to understand the impact on the risk of uncertainty associated with assay performance, especially when the available assay has not been evaluated using the blood samples collected in Puerto Rico post Zika outbreak.
5. Additional assessment of benefit-risk in term of hospitalized dengue cases may help understanding the disease burden on the public health system. However, clinical threshold for hospitalization may vary by countries. Therefore, benefit-risk of vaccination in term of hospitalized cases may vary by country partially due to difference in health care system and clinical practice.

FDA Benefit-Risk Assessment (for the Worst-Case Scenario of Assay Performance)

Inputs for FDA benefit-risk assessment are summarized in Table 1. Most of the inputs are same as those used by Sanofi, except for two inputs, Proportion of Dengue Negative among Zika Positive and Biocan RDT Cross-Reactivity to Zika Virus. The reasons for revision of these two inputs are discussed above. We first analyzed the prevented and excess severe dengue cases in Puerto Rico 9-16 years old population over 5-year post vaccination (Table 2). FDA estimated that 175 cases would be prevented, which is consistent with Sanofi's estimate. However, Sanofi estimated 4 excess severe dengue cases, while FDA estimated 7 cases. The discrepancy between these two estimates is mainly due to the different assumptions on percentage Puerto Rico population being Zika seropositive and Dengue seronegative. This portion of population is subjected to false positive for prior dengue exposure due to assay cross-reactivity. FDA considered 44% percent for this input more plausible and conservative than Sanofi's assumption. FDA risk assessment results indicate the likelihood of prevented severe dengue

cases among seropositive vaccinees of 9-16 years old in Puerto Rico is 73 cases per 100,000, and the likelihood of excess severe dengue cases among seronegative vaccinees of this age group is 37 cases per 1,000,000.

We also estimated the prevented and excess hospitalized dengue cases in Puerto Rico 9-16 years old population over 5-year post vaccination (Table 3). Based on information presented by CDC, about 1-5% of symptomatic patients had severe dengue and 10-20% of symptomatic patients were hospitalized due to dengue infection (VRBPAC, March 2019). The clinical trial data presented by Sanofi (Type C meeting slides, May 3, 2018) indicates that the hospitalized cases were about 4-6 times of the severe dengue cases. In our analysis we assumed number of hospitalized dengue cases is 5 times the severe dengue cases. However, it is important to point out that the rate of hospitalization may vary by countries due to difference in clinical practice. The difference in number of hospitalized cases may not be entirely attributable to benefit-risk of vaccination.

FDA had also conducted benefit-risk assessment for target age group of 9 through 45 years old initially proposed by Sanofi. The indication was changed to limit the vaccine use among the 9 through 16 years of age after March 2019 VRBPAC. The FDA benefit-risk assessment for 9 through 45 years old assumed the likelihood of prevented or excess cases of severe/hospitalized dengue cases are same as the age of 9 through 16 years old. The benefit-risk results for the population with wider age range are presented in Table 4 and 5.

Conclusions and limitations:

Overall, we agree with Sanofi on static approach for benefit-risk assessment. However, it is important to emphasize that populations with and without prior dengue exposure have distinct benefit-risk profiles for vaccination with Dengvaxia. For vaccine target population, who have prior dengue exposure, the benefit outweighs the risk. An estimate of 175 severe dengue cases may be prevented in 5 years among the seropositive population of 9-16 years old. However, for the same age population without prior dengue exposure, there is no benefit but increased risk of excess cases of severe and/or hospitalized dengue if they are inadvertently vaccinated as the result of false positive test results and subsequently exposed to wild type dengue virus. Approximately, 7 excess severe dengue cases may occur in 5 years among the vaccine target population.

There are limitations associated with both Sanofi and FDA's benefit-risk assessment. Though use of Dengvaxia is contingent upon a screen-and-vaccinate approach, there is no FDA approved or cleared serotest at this time to identify previous dengue infection in an asymptomatic individual who does not have a medical record of previous laboratory-confirmed dengue infection. The benefit-risk analyses are based on seroprevalence and the performance of serotests currently available in Puerto Rico. One of the greatest uncertainties is associated with the performance of commercially available pre-vaccination screening assays in Puerto Rico. Currently reported sensitivity was evaluated using blood samples from acute cases; thus, these assays were calibrated for the diagnosis of symptomatic patients (high titers). The sensitivity may be lower when the assay is used to test prior exposure of asymptomatic individuals. Specificities of the assays were evaluated based on the blood panel collected mainly outside of Puerto Rico (relatively small sample size for Puerto Rico). The specificity of the assay is likely lower when there is cocirculation of other flaviviruses in the vaccine target region such as Zika virus in Puerto Rico. There is limited flavivirus cross-reactivity data collected post-Zika outbreak. Available test performance data is reported by manufacturers and few tests have been assessed by independent party. Another great uncertainty is about seroprevalence of dengue and Zika among the vaccine target population in Puerto Rico. The data are limited. Seroprevalence varies by age group and changes over time depending on the local disease dynamics. Seroprevalence of dengue and Zika affect the performance of screening assay and has great impact on overall benefit-risk of Dengvaxia vaccination.

Reference:

Coudeville et al. Assessment of benefits and risks associated with dengue vaccination at the individual and population levels: a dynamic modeling approach. *Expert Rev Vaccines*. 2018 Aug;17(8):753-763.

Rosenberg et al. Vital Signs: Trends in Reported Vectorborne Disease Cases —United States and Territories, 2004–2016. *Morbidity and Mortality Weekly Report*. May 1, 2018.

FDA Vaccines and Related Biological Products Advisory Committee meeting. March 22, 2019.

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm630701.htm>

Table 1. Input Summary (the worst-case scenario)

Input Valuables	Input Values	
	FDA	Sanofi
Population of 9-16 year old	430,000	same
Population of 9-45 year old	2,500,000	n/a
Vaccination coverage	100%	same
Dengue seroprevalence	56%	same
Zika seroprevalence	25%	same
Proportion of Dengue negative among Zika positive	44%	13%
Biocan RDT sensitivity	60% (lower bound)	same
Biocan RDT specificity	97.4% (lower bound)	same
Biocan RDT cross-reactivity to Zika virus	8% (upper bound)	2.6% (mean)
Difference of 5-year severe dengue incidence between vaccination and placebo groups of individuals being seropositive at baseline	-0.121%	same
Difference of 5-year severe dengue incidence between vaccination and placebo groups of individuals being seronegative at baseline	0.074%	same
Ratio of hospitalized cases over severe dengue cases	5	n/a

Table 2. Estimate of Prevented (Benefit) and Excess (Risk) Severe Dengue Cases of Puerto Rico 9-16 Year Old Population within 5-Year Post Vaccination of Dengvaxia (the Worst-Case Scenario of Assay Performance)

		Benefit (Prevented Severe Dengue Cases)		Risk (Excess Severe Dengue Cases)			
	Population	Prevented Cases	Likelihood of prevented case	Excess Cases (non-cross reactivity)	Excess Cases (cross reactivity)	Total Excess cases	Likelihood of excessive case
Prior dengue exposure	430,000 x 56% =240,800	240,800 x 60% x 0.121% = 175	175/240,800 = 73 cases per 100,000	0	0	0	0
No prior dengue exposure	430,000 x 44% =189,200	0	0	189,200 x (1-97.4%) x 0.074% = 4	189,200 x 25% x 8% x 0.074% = 3	7	(4+3)/189,200 = 37 cases per 1,000,000
Total 9-16 year old population	430,000	175	175/430,000 = 41 cases per 100,000	4	3	7	(4+3)/430,000 = 16 cases per 1,000,000

Table 3. Estimate of Prevented (Benefit) and Excess (Risk) Hospitalized Dengue Cases of Puerto Rico 9-16 Year Old Population within 5-Year Post Vaccination of Dengvaxia (the Worst-Case Scenario of Assay Performance)

	Population	Benefit		Risk	
		*Likelihood of case prevented	Prevented cases	*Likelihood of excess cases	Excess cases
Prior dengue exposure	240,800	365 cases per 100,000	175x5= 875	0	0
No prior dengue exposure	189,200	0	0	185 cases per 1,000,000	7x5= 35
Total 9-16 year old population	430,000	205 cases per 100,000	875	80 cases per 1,000,000	35

*The excess hospitalized cases are assumed being 5 times of severe cases.

Table 4. Estimate of Prevented (Benefit) and Excess (Risk) Severe Dengue Cases of Puerto Rico 9-45 Year Old Population within 5-Year Post Vaccination of Dengvaxia (the Worst-Case Scenario of Assay Performance)

	Population	Benefit		Risk	
		*Likelihood of case prevented	Prevented cases	*Likelihood of excess cases	Excess cases
Prior dengue exposure	2,500,000 x 56% =1,400,000	73 cases per 100,000	1,400,000 x 73 per 100,000 = 1022	0	0
No prior dengue exposure	2,500,000 x 44% =1,100,000	0	0	37 cases per 1,000,000	1,100,000 x 37 per 1,000,000 = 41
Total 9-45 year old population	2,500,000	41 cases per 100,000	1022	16 cases per 1,000,000	41

*the likelihood of prevented and that of excessive severe dengue case in 9-45 years old are assumed same as those for 9-16 year old population.

Table 5. Estimate of Prevented (Benefit) and Excess (Risk) Hospitalized Dengue Cases of Puerto Rico 9-45 Year Old Population within 5-Year Post Vaccination of Dengvaxia (the Worst-Case Scenario of Assay Performance)

	Population	Benefit		Risk	
		*Likelihood of case prevented	Prevented cases	*Likelihood of excess cases	Excess cases
Prior dengue exposure	1,400,000	365 cases per 100,000	1022x5=5100	0	0
No prior dengue exposure	1,100,000	0	0	185 cases per 1,000,000	41x5=205
Total 9-45 year old population	2,500,000	205 cases per 100,000	1022x5=5100	80 cases per 1,000,000	41x5=205

* the number of hospitalized cases is assumed being 5 times of the severe dengue cases.