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Through: Robert Ball, MD, MPH, ScM
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Re: Surveillance for Rates of Hib Disease Among Persons Aged 0-4 Years Receiving Pentacel® or Other Hib Vaccines

Summary

Sanofi pasteur has submitted a protocol concept (code M5A15) for a post-marketing surveillance study to evaluate the effectiveness of invasive *Haemophilus influenzae* type b (Hib) disease among persons vaccinated with Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (Pentacel®) [DTaP-IPV/Hib]. The study will be carried out for a 6-year period (2008-2013) within the Centers for Disease Control and Prevention (CDC)'s Active Bacterial Core Surveillance (ABCs) program. The study objectives are to monitor the occurrence of invasive Hib disease over time following the introduction of Pentacel vaccine and to determine product-specific rates of invasive Hib disease within the monitored population. Control Hib vaccines include Sanofi Pasteur's stand-alone Hib vaccine ActHib and Merck & Co's PedVaxHib and Comvax (combined Hib and hepatitis B) vaccines. The study population will consist of persons aged < 5 years under the ABCs catchment area. Annual estimates of the study population and its vaccination history will be obtained, respectively, using the US Census Bureau data and data collected through sample surveys conducted by a national sampling organization. Data on breakthrough invasive Hib disease cases (defined at least 3 doses of Pentacel or stand-alone Hib vaccines) will be obtained through ABCs program. The total projected study population at the end of study is approximately over 10 million person-years. Based on the assumptions of 50% Pentacel market share, cumulative study population size (ranging from 0.5 million person-years in year 1 to approximately 10 million person-years in year 6), and rates of invasive Hib disease for breakthrough cases from 2000-2005 ABCs data (0.34 per 1 million person-years), power calculations were provided and ranged from 35% (RR=6 in year 4) to 81% (RR=9 in year 6). See table below.

Alternate Scenario 1: Only breakthrough cases are modelled.

Cohort Power (50% Pentacel Market Share)*

					RR=6 **		RR=7 **		RR=8 **		RR=9 **	
Year of Study	Projected Cumulative Cases	Cumulative Person-years	Projected SOC Rate per 100,000	Pentacel Cumulative Person-years	Pentacel Rate per 100,000	Power	Pentacel Rate per 100,000	Power	Pentacel Rate per 100,000	Power	Pentacel Rate per 100,000	Power
2008	0.00	509,141	0.000	254,571	0.000	NA	0.000	NA	0.000	NA	0.000	NA
2009	0.00	1,529,110	0.000	764,555	0.000	NA	0.000	NA	0.000	NA	0.000	NA
2010	0.00	3,072,367	0.000	1,536,183	0.000	NA	0.000	NA	0.000	NA	0.000	NA
2011	0.88	5,140,382	0.017	2,570,191	0.103	34.79%	0.120	40.52%	0.137	46.98%	0.154	51.12%
2012	1.78	7,738,292	0.023	3,869,146	0.138	55.50%	0.161	63.92%	0.184	71.09%	0.207	77.08%
2013	2.68	10,358,440	0.026	5,179,220	0.155	59.90%	0.181	68.53%	0.207	75.65%	0.233	81.39%

* Calculated assuming alpha = .10 (one-sided 95% CI) and uncorrected Chi-Square calculation using program (Dupont and Plummer)

** All of these calculations are based on asymptotic approximations that may not be valid given the spareness of the data. The Poisson approach as described in the preceding worksheet may be a more appropriate way of making inferences with these data.

NOTE: 50% market share beginning in 2008 was modeled, based on the market penetration spreadsheet ("Market %") and the assumption that marketing would begin by July 2007

General Comment(s)

- Please note that the evaluation for the immunogenicity of Pentacel Hib antigen (anti-PRP) failed to reach the non-inferiority criteria during the pre-licensure clinical trials. Although post-marketing observational studies evaluate the effectiveness of a drug or a vaccine in a real-life setting, these studies have several limitations including non-randomization of the study population and uncontrolled exposure and outcome assessment. Also, these types of study are subject to confounding, effect modification, and other bias, which may make the results of observational studies more difficult to interpret than the results of clinical trials. Observed differences for the Hib disease rates among Pentacel and other Hib vaccine recipients might be due to factors (e.g., socio-demographic characteristics, health care access, geographical location, Hib disease detection and reporting, etc) other than the vaccine effect. Such confounding factors could have been minimized by prospective, randomized and controlled clinical trials. Therefore, findings from these observational studies might not be appropriate to support comparison of product-specific rates of invasive Hib disease among different manufacturers' vaccines (e.g., the rate of invasive Hib disease among Pentacel recipients and the rate of invasive Hib disease among PedVaxHib or Comvax vaccine recipients) as proposed by Sanofi Pasteur.
- Please note that the incidence rates of invasive Hib disease (per 100,000 persons aged < 5 years) have been low both in Canada and in USA since the introduction of Hib vaccines. However, data from Notifiable Diseases Reporting System, Public Health Agency of Canada (a national, passive surveillance) and US CDC's ABCs program (an active surveillance involving 10 U.S. states) showed that the Canadian rates have been consistently higher than the US rates during 1997 – 2005 with the exception of year 1999 [see tables 1 and 2 below]. Although several

factors (e.g., surveillance system attributes, disease case definition and diagnosis, vaccination coverage, reporting compliance, population under surveillance, etc) might account for the rate difference in the two countries, it is likely there was an underestimate of the rate difference since Canadian data was obtained from a passive surveillance, which has limitations such as underreporting. Survey data provided by the sponsor showed that Canadian and US estimated vaccine coverage for 3-dose series of DTaP, IPV and Hib were above 90% in 2002.

- Please note that a representative of Sanofi Pasteur is listed as one of the lead investigators in this post-marketing study, which determine the rates of invasive Hib disease for Sanofi Pasteur's and Merck & Co's vaccines. This can represent a conflict of interest because the study might be conducted under undue influences of the sponsor.
- Please note that calculations of the study statistical power to detect relative risks ranging from RR=6 to RR=9 during different phases of study period (year 1 through year 6) were based, among other factors, on 50% Pentacel market share. These calculations might not be valid according to the following statement "All of these calculations are based on asymptotic approximations that may not be valid given the spareness of the data" stated in the protocol concept. The study only has adequate power (80% or more) to detect a RR=9 in year 6. According to the power calculations, please note that the risk for invasive Hib disease in the Pentacel recipient group might be 9 times as great as the risk in the other Hib vaccine recipient group and such risk can not be timely detected. As the rate of breakthrough invasive Hib disease among children aged < 5 years is rare (e.g., 2000-2005 ABC data: 3-5 cases/14 million person-year), it can require extremely large study population or long study period (which undermines the feasibility of the study) to evaluate the effectiveness of Hib component of Pentacel vaccine. Please see table 3 below for examples of study sample size. Because observational studies are not randomized and are subject to selection bias, conclusions regarding "non-inferiority" or "equivalency" [e.g., the experimental treatment is not clinically worse than (non-inferior) or clinically similar to (equivalent) a control active treatment] from these studies should be interpreted with caution. In order to assure adequate statistical power to detect an acceptable risk, the size of the study population for each of the study group should be determined before the implementation of the study.

Question(s) to Sponsor

- Please provide the statistical reasoning that yielded the provided cohort power (50% Pentacel Market Share) calculation.
- Vaccination history of study population will be obtained through sample surveys. Please provide more precise description of the survey sampling methodology and its accuracy in assessing the vaccine exposure in the study population.

Table 1. Invasive Hib Disease Rate per 100,000 Persons Aged < 5 Years, 1997-2005, USA.

	1997	1998	1999	2000	2001	2002	2003	2004	2005
USA ABC	0.60	0.20	0.60	0.20	0.10	0.10	0.20	0.15	0.14

Source: Active Bacterial Core Surveillance (ABCs), US Centers for Disease Control and Prevention.

Table 2. Invasive Hib Disease Rate per 100,000 Persons Aged < 5 Years, 1997-2005, Canada.

	1997	1998	1999	2000	2001	2002	2003	2004	2005
Canada online NDRS	1.33	0.75	0.36	0.41	0.74	0.71	0.48	0.39	0.44

Source: Notifiable Diseases Reporting System, Public Health Agency of Canada (data for 2003-2005 are provisional).

Table 3. Crude estimates of study population size if the null hypothesis $R = R_0$ vs alternative hypothesis of $R \neq R_0$

A	B	C	D	E	F	G	H	I	J	K
50% Market Share	R	R_0	Breakthrough Invasive Hib Disease Rate		Number of Person-years		Number of Cases		Total Number of Cases	Total Number of Person-years
			Pentacel	Other Hib vaccines	Pentacel	Other Hib vaccines	Pentacel	Other Hib vaccines		
0.5	1.1	1	0.00000022	0.00000020	1,313,288,754	1,313,288,754	289	263	552	2,626,577,508
0.5	1.2	1	0.00000024	0.00000020	343,956,575	343,956,575	83	69	152	687,913,150
0.5	1.3	1	0.00000026	0.00000020	159,818,205	159,818,205	42	32	74	319,636,410
0.5	1.4	1	0.00000028	0.00000020	93,806,337	93,806,337	26	19	45	187,612,674
0.5	1.5	1	0.00000030	0.00000020	62,537,558	62,537,558	19	13	32	125,075,116
0.5	1.6	1	0.00000032	0.00000020	45,166,014	45,166,014	14	9	23	90,332,028
0.5	1.7	1	0.00000034	0.00000020	34,459,470	34,459,470	12	7	19	68,918,940
0.5	1.8	1	0.00000036	0.00000020	27,360,181	27,360,181	10	5	15	54,720,362
0.5	1.9	1	0.00000038	0.00000020	22,389,989	22,389,989	9	4	13	44,779,978
0.5	2.0	1	0.00000040	0.00000020	18,761,267	18,761,267	8	4	12	37,522,534

Note: This table provides crude estimates of the study sample sizes [column K] based on 1) 50%Pentacel market share [column A], 2) background rate of breakthrough invasive Hib disease of 0.2 per 1,000,000 person-years (2000-2005 ABCs Surveillance System: 3 cases / 14,577,722 person-years) for other Hib vaccine group [column E], 3) 80% statistical power, and 4) the null hypothesis of $R = R_0$ vs alternative hypothesis of $R \neq R_0$ at a significance level of 0.05, where R [column B] is the ratio of invasive Hib disease risk in the Pentacel group [column D] to invasive Hib disease risk in the other Hib vaccine group [column E] and $R_0 = 1$ [column C], when the invasive Hib disease risk in the Pentacel group is the same as in the other Hib vaccine group. The total number of person-years needed ranges from approximately 37 million person-years to approximately 2.6 billion person-years.