

# Approaches to Licensure of Meningococcal Vaccines for Prevention of Serogroup B Invasive Meningococcal Disease

## Briefing Document for the Vaccines and Related Biologic Products Advisory Committee Meeting, April 7, 2011

### I. INTRODUCTION

Group B *N. meningitidis* is a significant cause of endemic and epidemic meningococcal disease worldwide. In the US, the annual incidence of meningococcal disease was 0.53/100,000 population from 1998 to 2007. Group B isolates cause approximately one third of invasive meningococcal disease overall, and over half of the disease in children under one year of age. Epidemics of group B disease have occurred recently in New Zealand and Brazil, and serogroup B accounts for most meningococcal disease in several countries in Europe.

Group B capsular polysaccharide (PS) is poorly immunogenic, even when conjugated to immunogenic carrier proteins, but investigations using group B meningococcal sub-capsular antigens in preventive vaccines have been promising. Among these, outer membrane vesicle (OMV) vaccines have been studied extensively and have been used previously in several countries as a public health measure to control specific outbreaks or epidemics (see below Section II). Accumulated experience indicates that OMV vaccines are efficacious, but the short duration of protection and narrow strain specificity may limit their usefulness. Clinical efficacy and post-implementation effectiveness studies in Chile, Cuba, Brazil, Norway and New Zealand indicate that OMV vaccines stimulate protective immune responses that correlate with functional bactericidal immune responses, but the strength and breadth of the immune response is age- and dose-dependent.

In addition to OMV vaccines, novel antigens have been identified using genomic and proteomic discovery tools in an attempt to extend the coverage to include a broad range of endemic serogroup B isolates. -----(b)(4)-----.

#### Issues for Evaluating the Efficacy of Meningococcal Protein Vaccines

The highest age-related disease incidence of group B meningococcal disease in the US is in children under one year of age. The annual incidence has declined from 3.3/100,000 to 1.79/100,000 in infants less than 12 months of age during the 10 years from 1998 to 2007. Serogroup C, Y and W-135 disease incidence in infants under 12 months of age ranged from 5.69/100,000 in 1998 to 1.07/100,000 in 2007 [1]. Traditional placebo-controlled efficacy studies for meningococcal protein vaccines would require a sample size that is considered unfeasible pre-licensure - on the order of several hundred thousand to over one million participants depending on specific incidence rates.

Serologic assessment of immune responses may be used to infer efficacy when there is ample scientific evidence to support a particular immune measure as a valid biomarker of a protective immune response. Historical data regarding human complement serum bactericidal activity (hSBA) assays have been discussed in previous meetings of the VRBPAC and in Session 1 of this meeting. Extensive experimental and epidemiologic data support complement-mediated bactericidal activity as the predominant mechanism of human protection from invasive meningococcal disease. Individuals who have circulating antibody that efficiently triggers complement-mediated bacterial killing are

protected from disease (see below Section II). Although other immune mechanisms may contribute to protection from meningococcal disease, none have been shown to be relevant to individual protection or contribute to vaccine efficacy in humans. Importantly, studies of PS, PS-protein conjugate and OMV vaccines have shown that meaningful information about vaccine-induced antibody-dependent complement-mediated bacterial killing can be obtained from hSBA assays.

Group B meningococcal OMV vaccine efficacy has been evaluated during epidemics that are predominantly clonal when the disease strain was used for preparation of the vaccine. In that context, the use of hSBA as an immune measure for group B vaccines is well-supported. Three efficacy studies of OMV vaccines were conducted between 1987 and 1991: a vaccine developed by Walter Reed Army Institute of Research (WRAIR) was tested in Iquique, Chile; an OMV vaccine produced by the Finlay Institute (VA-MENGO BC) was tested in Cuba; and an OMV vaccine developed by the Norwegian National Institute of Public Health (NIPH) was tested in teenagers in Norway [2-4]. In addition, a case-control study of the Cuban vaccine used in Brazil [5], and post-implementation estimates of effectiveness in New Zealand [20, 21], support the strain-specific effectiveness of OMV vaccines. Similarly, a correlation between hSBA seroresponse and disease protection has been shown when the target strain used in the assay is the same as the strain that is causing invasive disease. The overall effectiveness of vaccines that are designed to prevent diverse endemic meningococcal disease will depend on the proportion of circulating disease isolates that are susceptible to killing by vaccine induced functional antibody. The evaluation of vaccine effectiveness will require evidence that bridges functional immune responses measured using specific hSBA assay strains to protection against a highly diverse population of strains.

#### **Purpose and Focus of the April VRBPAC Meeting**

At the April 7, 2011 VRBPAC meeting, CBER will present historical evidence that supports the use of hSBA as a surrogate of protection in the context of protein-based vaccines used to address predominantly clonal group B meningococcal disease. The primary focus of the session will be to discuss approaches for evaluating the effectiveness of non-capsular vaccines that are under investigation for prevention of invasive disease caused by serogroup B strains of *N. meningitidis*. The current epidemiology of group B meningococcal disease and the molecular epidemiology of specific novel vaccine antigens in the U. S. and worldwide will be reviewed.

CBER will present and discuss the essential components of a strategy that, given the current state of knowledge, would be necessary to bridge human immunogenicity data to support approval of novel sub-capsular meningococcal vaccines. A well-defined strategy for the evaluation of vaccine effectiveness for prevention of invasive group B meningococcal disease will provide manufacturers with a possible pathway to follow during clinical development of novel vaccines for this indication. Sponsors have sought guidance from CBER regarding strategies for effectiveness evaluation to facilitate design and execution of the pivotal clinical trials that will serve as the basis of approval of sub-capsular meningococcal vaccines. While CBER considers the proposed strategy presented in this document an appropriate one, we remain willing to accept and evaluate any scientifically sound strategy proposed by applicants. We seek input and discussion from VRBPAC regarding the strategy discussed below.

## II. OUTER MEMBRANE VESICLE VACCINES

### Clinical efficacy

Four OMV vaccines have been developed, tested and used as public health measures to control specific outbreaks or epidemics of group B meningococcal disease:

WRAIR developed an outer membrane protein vaccine to control an epidemic in Chile that was caused by a B:15:P1.3 ET-5 complex strain. In the efficacy study, two doses of vaccine were given to persons 1 to 21 years of age. Protection was age-related with a point estimate for efficacy of 70% ( $P = 0.04$ ) after 30 months of observation for individuals 5 to 21 years of age, while no protection was observed for younger children [2].

In Cuba, VA-MENINGOC-BC was developed by the Finlay Institute to control an epidemic caused by a B:4:P1.19,15 ET-5 complex strain. The vaccine was given as two doses and tested in a randomized, double-blind controlled trial in 106,000 Cuban students (aged 10 to 14 years). Strain-specific efficacy was 83% during the 16 month observation period (95% confidence interval (CI) 42–95%) [3]. In a case-control study in Sao Paulo, Brazil, two doses of VA-MENINGOC-BC were given to all age-groups. Effectiveness estimates (95% CI) of -37% (-100–73%), 47% (-72–84%) and 74% (16–92%), were calculated for groups of infants aged 3 to 23 months, 24 to 47 months and 48 to 83 months, respectively [5].

In Norway, MenBvac was developed by NIPH in response to a clonal epidemic caused by a B:15:P1.7, ST-32/ET-5 strain. The efficacy trial of two doses of MenBvac in 172,800 students aged 13–14 years showed a protection rate of 57% (95% CI = 21–87%) over the 29 month observation period [4]. However, most cases in the vaccine group occurred later than in the placebo group, and an interim protection rate of 87% (95% CI = 62–100%) was estimated for the first 10 months [6].

Overall, these OMV vaccines showed clinical protective efficacy in older children or teenagers using a 2-dose regimen. The clinical trials in Cuba and Norway were placebo-controlled trials and the point estimates were 83% and 57%, over observation periods of 16 months and 29 months, respectively. In the Norwegian study, the relatively high (87%) interim efficacy at 10 months suggests that additional benefit might be obtained from a booster dose. In both of these large studies the numbers of disease cases that occurred were relatively few, so the confidence intervals are wide.

### Measures of group B meningococcal vaccine immunogenicity

Two principle methods have been used to measure immune responses to meningococcal vaccines. ELISA, using OMV from the vaccine strain as the coating antigen, measures anti-OMV antibody concentration. SBA assays measure functional antibody by determining the ability of sera to kill a target *N. meningitidis* strain via complement-mediated bacterial cell lysis. There are several types of SBA assays, but all involve incubating a bacterial cell suspension with sera and an active complement source. Surviving bacteria are quantified, usually by colony counts, and compared to either the cell count prior to killing or a control in which the complement was heat inactivated. Antibody concentration does not correlate with functional activity, especially in young children.

The source of complement is a critical factor for SBA. Intrinsic bactericidal activity is determined using the complement activity of test sera, usually at a single 1:4 dilution. This method was used in some of the original studies by Goldschneider et al. [7], but has not been used for OMV vaccine evaluation. For intrinsic activity, the sera must be tested at the time they are collected, or processed and stored in such a way as to preserve complement activity. More typically, quantitative

determinations are performed using two-fold serially diluted heat inactivated test sera with an extrinsic complement source added. Both human and animal, usually baby rabbit, complement (hSBA and rSBA, respectively) are used to measure SBA responses to PS vaccines. For testing the bactericidal activity of human sera against group B *N. meningitidis* strains, only human complement is suitable. The complement source is often not described in published reports. When stated, a single human sera that was not bactericidal to the target strain was most often used to evaluate OMV vaccine immunogenicity. It is recognized that assay results can vary depending on the individual complement source.

The 1:4 threshold of protection often cited was based on the observation that individuals with intrinsic killing of a circulating group C *N. meningitidis* strain measured at a dilution of 1:4 did not develop disease, even when exposure to the organism was documented by throat culture [7]. The intrinsic assay has not been formally compared to the current hSBA assay, but most studies describe the proportion of sera with a positive titer ( $\geq 1:4$ ), seroresponse ( $\geq$  four-fold rise) and geometric mean SBA titer (GMT). Most SBA assays start at a dilution of 1:4, so a threshold of 1:8 accounts for assay variability and allows an accurate evaluation of precision at the threshold titer.

### **OMV vaccine immunogenicity – hSBA correlation with protection**

The proportions of vaccinees with  $\geq 4$ -fold rises in hSBA pre- to post-vaccination or with hSBA titers  $\geq 1:4$  or  $\geq 1:8$  have been correlated with the clinical efficacy of OMV vaccines. In Norway, phase II trials showed that more than 80% of vaccinees developed bactericidal antibodies following vaccination. Consistent with the observed efficacy, bactericidal antibody levels waned after 10 months [4, 7]. In Chile and Brazil, little or no protective effect was seen in children under 4 years of age [5, 8, 9]. Protection correlated with the appearance of serum bactericidal activity, but not with anti-OMV IgG antibody responses measured by ELISA, which were highest in the youngest age groups [8].

Subsequent studies were conducted to examine the immunologic basis for protection following OMV vaccination, and the potential for improved responses in both children and adults. These studies showed that OMV vaccination induced priming, and that boosting occurred following a third dose administered as late as 4 or 5 years after the primary series [10-12]. The advantage of a third dose was confirmed in a randomized immunogenicity study in Iceland in which a booster dose at 10 months resulted in significantly increased bactericidal responses [13].

Age-dependent differences in the immune responses after immunization with OMV vaccines were evaluated in a collaborative trial in Santiago, Chile in 1994 with the Cuban and Norwegian OMV vaccines administered as a three dose series [14]. This study showed that over 90% of infants less than 1 year of age developed a  $\geq 4$ -fold increase in hSBA titer against the respective vaccine strain following the third dose suggesting that strain-specific protection in young infants could be achieved. However, when the target strain differed from the vaccine strain (i.e., the heterologous OMV strain), only 10% of the infants were counted as responders, compared to 45-60% of adults.

### **New Zealand OMV experience**

To address an epidemic in New Zealand, an OMV vaccine based on the B:4:P1.7-2 epidemic strain (NZ 98/254) was developed. Based on the previous experience with OMV vaccines, it was considered unethical in New Zealand to undertake a placebo-controlled phase III clinical trial. Instead, randomized observer-blind safety and immunogenicity trials of MeNZB were used to evaluate the vaccine. Immunogenicity was determined as a four-fold rise in hSBA levels following vaccination, or a minimum post-vaccination titer of 1:8 from a pre-vaccination titer of  $< 1:4$ . Interpolated titer values

based on the percentage kill in the dilutions on either side of the 50% kill point were used, and an inter-laboratory study involving NIPH, the Health Protection Agency Manchester Laboratory, Chiron and the New Zealand Institute of Environmental Science and Research provided the basis for protocol development and test experience [15, 16]. For participants from 6 months of age to adults (6–8 months, 16–24 months, 8–12 years and >18 years), the percentage of responders (titer  $\geq 1:8$ ) following 3 doses were 74–75%, and the percentage of those achieving a titer  $\geq 1:4$  were higher than 90% for each age group [17, 18].

MeNZB was approved by the New Zealand Regulatory Authorities for epidemic control and campaign use in July 2004 [19]. As a public health intervention, MeNZB was administered to all individuals between 6 weeks and 19 years. Approximately 1 million people were given three doses at 6-week intervals. Young infants received a 4<sup>th</sup> dose at 10 months of age. The initial estimation of MeNZB effectiveness in a prospective study using a generalized estimating equation model to compare rates of disease in vaccinated and unvaccinated populations was 73% (95% CI = 52–85%) [20]. Effectiveness in children aged 6 months to <5 years was later estimated by an observational cohort design [21] in which fully vaccinated children were found to be 5 to 6 times less likely than unvaccinated children to contract meningococcal disease caused by the epidemic strain in the 24 months after immunization. This corresponded to a vaccine effectiveness of approximately 80%.

The New Zealand experience supports the relationship between immunogenicity as measured by hSBA seroresponse and OMV vaccine effectiveness. The ability to induce a protective immune response by using three doses in infants, first shown in the Tappero study [14], was confirmed in the New Zealand immunogenicity studies [17, 18] and supported by post-implementation estimates of effectiveness. In addition, the dominant immune response to the outer membrane protein PorA was also observed in New Zealand. Deletions in the PorA variable region (VR) 2 epitope of the New Zealand epidemic strain modified the level of strain recognition by vaccine-induced functional antibodies. Impaired expression of the PorA protein in an epidemic strain type, due to a reduction of guanidine residues in the poly-guanidine track of the *porA* promoter region, resulted in no serum antibody recognition in the hSBA assay [22].

### **III. N. MENINGITIDIS STRAIN DIVERSITY**

The design and evaluation of protein-based meningococcal vaccines is complicated by the level of genetic and antigenic diversity found among meningococcal invasive disease isolates.

#### **Strain classification**

*N. meningitidis* can be structured into clonal complexes which are groups of related strains defined by multilocus sequence type (MLST) analysis based on seven housekeeping genes. Sequence types (STs) that share a minimum of four identical alleles with a central (ancestral) ST are assigned to clonal complexes (CC). CC are remarkably stable. Genomic studies demonstrate that the majority of cases of invasive meningococcal disease are caused by isolates that belong to a limited number of CC known as hyper-invasive lineages [23–25].

Some meningococcal outer membrane (OM) protein structures and their respective genes form the basis of further classification schemes including type and subtype, based on genetic and antigenic differences in the major OM porin proteins PorB and PorA, respectively. The capsular polysaccharide (serogroup), OM proteins (OMPs) and lipo-oligosaccharide (LOS, immunotype) have been implicated in meningococcal virulence. Although some OMP types are associated with CC, OMP type cannot be accurately predicted by CC.

## Antigen variation

*Neisseria meningitidis* is naturally competent for transformation, which enables the horizontal exchange of DNA between strains, resulting in the mosaic structure of genetic loci. Antigenic changes in OMPs are often mediated through horizontal gene transfer. Large DNA sequences may also be acquired through horizontal gene transfer. For example, genetically identical meningococcal serogroup B and C disease isolates were identified in the Pacific Northwest that differed only in their capsular polysaccharides; this phenomenon is known as capsular switching. A recent study has demonstrated that commensal *Neisseria* have an extensive repertoire of virulence alleles from pathogenic *Neisseria* as well as other bacterial genera, and nearly half of *Neisseria* virulence genes have undergone intra- and inter-species recombination. This suggests that high-frequency horizontal gene transfer can increase pathogen fitness, accelerate host adaptation and affect bacterial virulence [26-28].

Additional mechanisms of variation include repetitive sequences and phase variation. Addition or subtraction of repeated units creates frameshifts and premature stop codons, or alters the strength of the promoter. Phase-variable genes in *N. meningitidis* include those involved in the biosynthesis of the capsule, LOS, pili, opacity proteins, PorA OMP, FetA and the neisserial adhesin A (NadA) [29]. There is also evidence that *N. meningitidis* possesses a phase-variable type III restriction–modification system that regulates the expression of multiple genes.

### Overview of PorA, fHBP, NadA and NHBA variation

PorA is the immunologically dominant antigen in OMV vaccines. Point mutations in PorA variable region (VR)1 and VR2 and the replacement of epitopes by recombination and small deletions contribute to antigenic variation in PorA. A point mutation generating a single amino acid change in the epitope can result in the loss of monoclonal antibody (mAb) binding and bactericidal killing. Loss of PorA expression may occur due to the insertion of *IS1301* in the coding region of PorA and/or deletion due to mispairing on the polyguanidine stretch or replacement of a poly(G) residue within the intervening sequence regions of the promoter. Phase variation of PorA may also provide a mechanism for evading the host immune system [30-34].

NadA is involved in binding and invasion of epithelial cells. There are five genetically distinct NadA protein variants. NadA1, NadA2 and NadA3 are immunologically cross-reactive, but are poorly cross-reactive with NadA-4 and NadA-5. The presence of *nadA* ranges from 0% (e.g., CC41/44) to 100% (e.g., CC32). Among isolates with *nadA*, the level of expression varies within and between isolates due to phase variation and transcriptional regulators [35-42].

Neisserial heparin-binding antigen (NHBA, also known as GNA2132) is a surface-exposed lipoprotein and is highly conserved in sequence and present across all strains tested. A recent study has revealed that NHBA may be an important virulence factor that binds glycosaminoglycans (e.g., heparan sulfate) that are present on the surface of host cells or released in mucous secretions, thus improving the survival of *N. meningitidis* in the human host. This antigen is recognized by sera of patients after meningococcal disease. Recent studies, however, suggest that this antigen may not induce independent bactericidal antibodies. The effect of NHBA sequence on antibody binding has not been extensively evaluated [40-43].

Factor H-binding protein (fHBP) is also known as LP2086 or GNA1870 [44-45]. fHBP binds to the alternative pathway inhibitor, fH, resulting in down regulation of the complement pathway and increased bacterial survival. fH also influences the classical complement pathway. Two classification systems for fHBP have been developed, one is divided into sequence variant groups 1, 2 and 3, and the

other designates subfamilies A (corresponding to variants 2 and 3) and B (corresponding to variant 1). Immunological cross-reactivity is good among subvariants within group 1, and some immunological cross-reactivity exists between variants 2 and 3; little cross-reactivity is seen between strains within group 1 and groups 2 or 3 [44-47]. fHBP alleles have been identified and classified from extensive collections of invasive disease isolates from the US, Europe, New Zealand and South Africa [37, 38, 40, 42, 48]. Among 143 serogroup B isolates tested for reactivity with six anti-fHBP mAbs by dot immunoblotting and for susceptibility to bactericidal activity of mouse antisera, isolates representative of five anti-fHBP mAb-binding phenotypes (70% of isolates) were highly susceptible to anti-fHBP variant 1 or variant 2 bactericidal activity. Recently an alternative classification was proposed based on a modular fHBP architecture, consisting of five variable segments that are combined resulting in one of nine modular groups. Mouse antisera to recombinant fHBP from each of the modular groups showed modular group-specific bactericidal activity against strains with low fHBP expression but broader activity against strains with higher fHBP expression. The bactericidal activity of sera from rabbits immunized with bivalent fHBP vaccine was dependent on the level of fHBP surface expression in 100 invasive serogroup B disease-causing isolates. Thus, both the sequence and the relative expression of fHBP may affect strain susceptibility to anti-fHBP bactericidal activity [38, 49-52].

The information currently available regarding both traditional and novel meningococcal vaccine antigens indicates that the evaluation of breadth of coverage for sub-capsular protein vaccines will be complex. Vaccine effectiveness will be affected by antigen sequence diversity and antigen expression diversity among circulating strains in the target population as well as by the prevalence, concentration and specificity of bactericidal antibodies induced by the component vaccine antigens. The susceptibility of any specific isolate to vaccine-induced bactericidal antibodies may be affected by the expression level of each vaccine antigen as well as expression of other uncharacterized surface components. The degree of cross-protection in an individual's response to vaccination is likely to be age- and dose-dependent.

#### **IV. BRIDGING SEROLOGIC RESPONSE TO VACCINE EFFECTIVENESS**

The evaluation of a vaccine for protective efficacy against all *N. meningitidis* strains that cause invasive disease is not possible. Meningococcal strains are diverse and evolve over time. There are clear differences in the magnitude, duration and breadth of immune responses between infants and older children or adults. The prevalence of disease in the US is not adequate to assess clinical efficacy directly, and the number of distinct strains that would need to be tested in hSBA assays to adequately represent US endemic disease would be unfeasible using current hSBA methodologies.

The assessment of immunogenicity and estimates of effectiveness are complicated by the presence of sequence and expression diversity of vaccine target antigens in isolates that are responsible for invasive meningococcal disease. However, there is evidence to support antibody-dependent complement-mediated bactericidal killing as the principle mechanism of human immunity to group B meningococcal disease, similar to other serogroups. Based on the experience with OMV vaccines, antibody to sub-capsular protein antigens can provide strain specific protection and can be accurately measured in hSBA assays using an extrinsic source of human complement. The correlation between hSBA seroresponse and vaccine efficacy is supported when invasive disease is caused by the same strain that is used for both vaccine preparation and serologic assessment.

Potential approaches to demonstrate effectiveness of group B meningococcal vaccine candidates that have been considered include evaluation of clinical efficacy in a geographic region and age group that has a higher incidence of invasive meningococcal disease. The molecular epidemiology of disease isolates would likely be different from the US, and high rates of disease generally occur only in the context of persistent clonal outbreaks or epidemics. Placebo-controlled efficacy trials would be

unlikely in such a scenario since the use of licensed PS-conjugate vaccines, or a strain specific OMV vaccine could be considered.

Also, direct determination of bactericidal activity of post-immune sera against a representative and epidemiologically relevant collection of disease isolates would allow a direct bridge from the serologic correlate to effectiveness. This approach is limited by the quantity of serum obtained in infant studies, and the need for individual external complement sources to be qualified for each test strain. It is not known if alternative methodologies such as “universal” complement sources (IgG depleted serum, or animal complement with the addition of specific human complement regulatory factors) would be suitable for clinical immunogenicity assays. Testing intrinsic bactericidal activity to determine the proportion of diverse strains that are killed pre- vs. post-immunization is complicated by the technical difficulty of collecting and storing intrinsically active sera. This approach also has not been used previously in clinical vaccine trials.

## **V. THE REGULATORY PATH FORWARD**

The path forward for licensure of sub-capsular vaccines for prevention of invasive meningococcal disease may be based on evidence of effectiveness inferred from immunogenicity. The immunologic evaluation of vaccine effectiveness for protection against diverse endemic meningococcal disease may consist of the following parameters:

a. *The use of hSBA as a correlate to predict protection.*

The available scientific evidence supports hSBA as a surrogate of strain specific protection for prevention of group B meningococcal disease. The relationship between hSBA and protection is not limited to the context of polysaccharide vaccines and anti-capsular antibody. CBER has advised vaccine manufacturers to develop hSBA assays that assess functional immune responses to each specific vaccine antigen. In doing so, manufacturers will need to consider factors such as encapsulation, antigen expression levels, prevalence of pre-immunization titers, availability of complement and resistance to non-specific killing of hSBA assay strains.

b. *Bridging of hSBA test strains to disease strains.*

Endemic group B meningococcal disease is caused by strains that are diverse with respect to the vaccine antigens that are under development. Thus, CBER has advised vaccine manufacturers to characterize the sequence and surface expression of the antigen in the hSBA test strains, and determine if the susceptibility of other strains to killing by vaccine antisera can be correlated with sequence similarity and surface expression density.

Manufacturers would need to provide scientific evidence that supports antigen characterization as a bridge between clinical trial hSBA immunogenicity data and predicted vaccine effectiveness for diverse disease isolates. This should include:

- Confirmation of the correlation between antigen sequence / expression level and susceptibility to killing by individual pre- and post-immune sera, not pooled sera
- Characterizing the relationship between antigen sequence / expression level and susceptibility to killing by age group (the estimated breadth of coverage may be different for infants than for older children or adults)

Finally the antigen characterization of a representative and epidemiologically relevant collection of disease isolates would be compared to the sequence and surface expression of the antigen in the hSBA test strain used in clinical immunogenicity assays.

c. *Post-marketing clinical effectiveness studies.*

The current epidemiology of meningococcal disease in the US precludes the conduct of pre-licensure efficacy studies. In addition, given the propensity for *N. meningitidis* to adapt via antigenic diversification, the molecular epidemiology of group B disease may change over time. Therefore we anticipate that studies to monitor the effectiveness of the vaccine post-licensure will be needed and will be part of future product specific licensing discussions.

On April 7, 2011, VRBPAC will be asked to advise on this proposed approach to licensure of meningococcal B vaccines, taking into consideration specific challenges for microbiologic bridging from hSBA test strain immunogenicity data to endemic meningococcal disease effectiveness. These challenges include:

- Development and validation of predictive microbiologic characterization tests of disease strains
  - Criteria for establishing correlation
  - Validation criteria
- Identification of relevant disease isolates
- Incorporation of bridging results into effectiveness estimates
  - To predict vaccine effectiveness, or
  - To restrict effectiveness claims (labeling)

## VI. CONCLUDING REMARKS

No group B meningococcal vaccine is currently licensed in the US. Placebo-controlled clinical endpoint efficacy studies in the US are considered not feasible because of low disease incidence rates and thus, sample sizes required would be prohibitively large. Although evaluation of clinical efficacy in a geographic region and age group with a higher incidence of invasive meningococcal disease has been considered, the molecular epidemiology of disease isolates would likely be different from the US providing challenges to the extrapolation of vaccine effectiveness. There is evidence that serum bactericidal antibodies may serve as a correlate to predict protection from group B meningococcal disease. However, the large number and diversity of group B meningococcal disease strains presents challenges to traditional testing, e.g., infant serum derived from clinical trials is limited and each strain tested requires specific assay development. Thus, use of pre-specified bactericidal antibody titers measured in a bactericidal assay coupled with an appropriate method to bridge hSBA test strains to disease strains as presented in this document is proposed for inferring effectiveness, and will be reviewed when VRBPAC convenes on April 7, 2011. The committee will be asked to advise on this proposed approach to licensure of group B meningococcal vaccines and also discuss the challenges for microbiologic bridging from hSBA test strain immunogenicity data to endemic meningococcal disease effectiveness. In addition, CBER is seeking advice from VRBPAC regarding any additional information that may be needed.

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