VRBPAC BRIEFING DOCUMENT

Licensure Strategies for Pneumococcal Conjugate Vaccines

March 8, 2001

Background

Streptococcus pneumoniae is an important cause of morbidity and mortality for infants and adults worldwide. In children less than 2 years of age, *S. pneumoniae* is a leading cause of meningitis and bacteremia. The annual incidence rates for pneumococcal bacteremia in the U.S. exceed 150 cases/100,000 population for children less than 2 years of age (Klein, 1995, Microb. Drug Resistance, 1:49-58; Butler, 1997, Microb. Drug Resistance, 3:125–129; Butler et al, 1995, J. Inf. Dis., 171:885-9).

S. pneumoniae is also an important cause of acute otitis media in young children, accounting for 20% - 48% of cases (Bluestone et al, 1992, Ped. Inf. Dis. J.;11, S7-1; Giebink GS, 1989, Ped. Inf. Dis. J.; 8: S18-20). The peak incidence of AOM occurs between 6-18 months of age (Teele et al, 1989, J. Inf. Dis. 160: 83-94). In developing countries *S. pneumoniae* acute respiratory infection is the leading contributor to the four to five million annual deaths in children under five years and *S. pneumoniae* is an important cause of death in children under two years (Klein, 1995, Microb. Drug Resistance, 1:49-58). The incidence of antibiotic resistant pneumococci has been on the rise since the 1980s. Based on a national sample of invasive pneumococcal isolates, resistance to penicillin (minimum inhibitory concentration [MIC] ≥ 2.0 ug/ml) has increased from 1.2% in 1992, to 13.6% in 1997 (Whitney et al, 2000, New Engl. J. Med., 343, 1917-1924). The 7 serotypes isolated most frequently from children less than 6 years of age also account

for about 80% of isolates not susceptible to penicillin (Butler, 1995, J. Inf. Dis.; 171:885-9).

Vaccines to protect children less than 2 years of age against *S. pneumoniae* diseases

The bacterial capsular polysaccharide vaccines that are licensed in the U.S. are poorly immunogenic in children less than 2 years of age and, therefore, are not recommended in this age group. However, coupling of the bacterial polysaccharides with protein carriers is thought to induce a T-cell dependent immune response after primary vaccination, and brisk increases in serum antibody levels upon repeated injections in young children. The development of *S. pneumoniae* polysaccharide conjugate vaccines has followed the successful example of Hib polysaccharide protein conjugate vaccines.

The Wyeth Lederle 7-valent pneumococcal conjugate vaccine (Prevnar™) was licensed by FDA on February 17, 2000. This vaccine is indicated to protect children less than 2 years of age against invasive pneumococcal disease caused by the seven serotypes included in the vaccine, i.e., 4, 6B, 9V, 14, 18C, 19F and 23F. Capsular polysaccharides from these serotypes are coupled to a non-toxic cross-reacting mutant diphtheria toxin molecule (CRM197). The prophylactic efficacy of Prevnar™ against invasive disease (bacteremia and meningitis) was demonstrated in a large field efficacy study, conducted at Northern California Kaiser Permanente (NCKP) health care system. A high level of efficacy in preventing vaccine serotype invasive pneumococcal disease was demonstrated in the primary analysis [100% (95% CI: 75, 100%)]. Similarly, efficacy in preventing

invasive disease due to all pneumococcal serotypes was 90% (95% CI 58,99%) (Black *et al*, 2000, *Pediatr. Infect. Dis*. J. 19:187-195). Published results of a clinical trial of Prevnar™ in prevention of acute otitis media (AOM) conducted in Finland showed that efficacy was 34% against all pneumococcal AOM and 57% (95% CI 44,67%) against vaccine-serotype AOM (Eskola *et al*, 2001, N. Engl. J. Med., 344, 403-408).

Pneumococcal conjugate vaccines with increased valency and/or combined with vaccine antigens from other bacterial organisms currently in clinical development

In order to increase the protection provided by pneumococcal conjugate vaccines to other prevalent pneumoccocci in the U.S. and worldwide, vaccine manufacturers have generated new pneumococcal conjugate vaccines that contain as many as 13 pneumococcal serotypes. These vaccines differ with regard to polysaccharide antigen concentration, the protein carrier chosen for conjugation, and vaccine valency. In addition, some are combined with vaccine antigens directed against non-pneumococcal pathogens. For some of these products, Phase 1 and 2 clinical studies are ongoing or completed.

CBER has received clinical development proposals from 4 vaccine manufacturers for new pneumococcal conjugate vaccines that include alternative approaches for obtaining approval. The proposals that the sponsors have submitted to CBER differ considerably among the manufacturers. Commercial sponsors will have the opportunity to present their most recent development plans in closed session at the March 8, 2001, VRBPAC meeting. In order to provide committee members with a sense of the clinical development strategies that manufactures have proposed

to CBER prior to the VRBPAC meeting, key elements of development plans are summarized below:

Sponsors have proposed to:

a. Conduct a non-inferiority study based on selected immune parameters for the 7 serotypes common to the new vaccines and Prevnar™
b. Conduct efficacy studies for an invasive disease endpoint, in a setting outside the U.S., where rates of invasive pneumococcal disease are relatively high;
c. Conduct or submit data from completed controlled efficacy trials for acute otitis media endpoints
d. Conduct or submit data from completed controlled efficacy trials for pneumonia endpoints.

All of the proposed clinical endpoint studies have been non-comparative trial designs, using placebo or unrelated vaccine antigen controls (e.g., Hep A, Hep B vaccine etc.).

It is important to note that some clinical development plans contain a combination of the various key elements outlined in the above items a-d. In some cases, more than one vaccine indication may be sought (e.g., invasive disease, AOM, pneumonia).

In addition to providing evidence of efficacy or non-inferiority for immune parameters or correlates, manufacturers will assess the following in clinical trials of pneumococcal conjugates: safety, lot consistency, and immune responses when administered

simultaneously with childhood vaccines used in the U.S. to support licensure.

Potential predictors of efficacy for pneumococcal vaccines

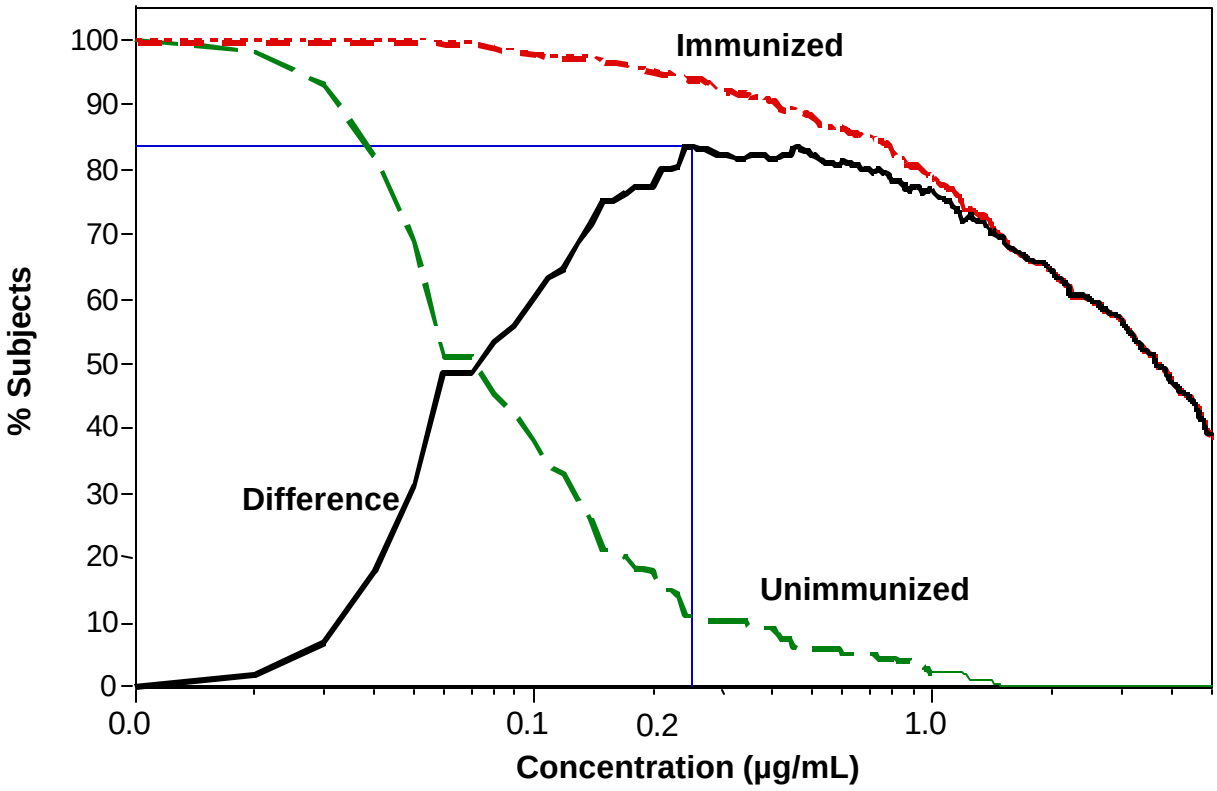
If licensure of pneumococcal conjugate vaccines is to be based on non-inferiority studies comparing immunologic responses, the parameters which best correlate with protection would need to be quantitatively defined. In the case of *Haemophilus influenzae*, protective antibody levels were established based on concentrations of antibody to polyribosylribitol phosphate (PRP) capsular antigen observed in individuals not developing clinical disease (Robbins et al, 1973, Pediatr. Res. 7:103-110; Kahty et al, 1983, J. Inf. Dis., 147:1100). Subsequently, quantitation of capsule specific antibody by ELISA has been used to assess the adequacy of immune responses to *Haemophilus influenzae* conjugate vaccines for the purpose of licensure. However, a correlate of protection against invasive disease could not be derived directly from the efficacy trials for Prevnar™. Therefore, preparatory to this advisory committee meeting, an FDA/NIAID sponsored workshop is planned for February 26, 2001, to discuss various immune parameters that could be used to assess non-inferiority of vaccine responses and serve as a basis for licensure. Workshop discussions will focus on defining, with regard to pneumococcal disease and pneumococcal conjugate vaccine-induced protection, the mechanism(s) of protective immunity and potential correlates of protection that could be used in non-inferiority studies. A synopsis of the outcome of the workshop will be presented to the advisory committee. Some immunologic parameters that are likely to be considered as a basis for a head-to-head comparison of new

pneumococcal conjugate vaccines and Prevnar™ are reviewed below. As noted above, a correlate of protection against invasive disease could not be derived directly from the efficacy trials for Prevnar™, due to the paucity of vaccine failures. Therefore, immune parameters less clearly associated with vaccine efficacy need to be considered.

At the VRBPAC meeting of 11/5/99, which was dedicated to the discussion of Prevnar™, results from a manufacturing bridging study were presented. Anti-pneumococcal responses between groups immunized with vaccines prepared at full manufacturing scale with those of a group immunized with a single lot prepared at pilot scale were compared based on the percent of subjects responding with antibody levels above specified threshold antibody concentrations. The chosen threshold antibody levels provided maximal discrimination between naive and immunized individuals at 7 months of age by determining concentrations where the <u>greatest</u> percentage of immunized individuals were above the threshold, and the <u>lowest</u> percentage of naive individuals were above the threshold. For Prevnar™, the threshold antibody levels ranged from 0.15 μg/mL for serotype 4, to 0.38 μg/mL for serotype 14. As an example, the choice of threshold value 0.25 μg/mL for serotype 6B, based on maximal discrimination of the immunized population is illustrated below (FDA presentation, VRBPAC 11/9/99).

Maximal Difference in GMC:
Immunized and Unimmunized Populations

Serotype 6B



Conceptually, the percentage of individuals with seroresponses above threshold antibody concentrations could be considered a criteria for establishing non-inferiority based on a head-to-head comparison of a new pneumococcal conjugate vaccine and Prevnar™. Clinical samples obtained from subjects immunized with either Prevnar™ or new pneumococcal conjugate

vaccine would need to be evaluated site-by-site using a standardized validated assay. The statistical criteria for comparability to Prevnar™ would need to be defined. Typically, criteria used for determining adequacy of bridging are:

a) ratio of the geometric mean antibody concentration (GMC) not less than 0.5 (lower bound of 90% CI) for non-inferiority of the new pneumococcal conjugate vaccine relative to Prevnar™
b) less than a 10 percentage point difference in proportions responding above a predefined antibody concentration or titer (lower bound of the 90% CI not less than –10% on the difference in proportions responding [the new pneumococcal conjugate vaccine minus Prevnar™]).

Sponsors have also proposed using a single antibody concentration cut-off to be used for all vaccine serotypes. If one accepts the threshold values as defined above to be meaningful, one might choose an antibody concentration at or above the highest threshold level observed for any one of the serotypes, such as 0.5 µg/mL, to assure that more stringent criteria are met for all serotypes.

Establishing non-inferiority based on seroresponse rates and GMCs vis-à-vis the licensed product, Prevnar™, could be a difficult standard to meet. With 7 serotypes and 2 sets of endpoint criteria, the statistical analysis is complicated by issues of multiplicity due to 14 comparisons. The probability of failure to demonstrate non-inferiority for one of the parameters increases with each comparison, and could be observed due to chance alone. Moreover, because Prevnar™ was highly

efficacious in preventing invasive disease, the antibody levels attained following Prevnar™ may be in excess of levels required for protection from invasive disease. Other vaccine formulations might still be effective, even if the antibody levels achieved are significantly lower than those achieved following Prevnar™. Nevertheless, in the absence of definitive data confirming protection associated with a particular serum antibody concentration, as determined by ELISA, comparability of new products to Prevnar™ provides the best assurance that the immune responses achieved by the new products are associated with protection.

Other immunological parameters could be at least as important as ELISA antibody levels. As opsonophagocytic antibodies are thought to play a central role in protecting against *S. pneumoniae*, determining vaccine-induced antibodies with opsono-phagocytic activity may also be a relevant study endpoint. Efforts have been directed towards developing a standardized assay to assess the opsonophagocytic activity of anti-pneumococcal antibodies (Romero-Steiner *et al*, 1997; Clin. Diag. Lab. Immunol. 4:414-422). Recent data suggest that higher avidity of IgG for *S. pneumoniae* capsular polysaccharides correlates with an increased ability of sera to mediate complement-dependent killing of the organism by phagocytosis (Romero-Steiner *et al*, 1999, Clin. Inf. Dis. 29:281-299). Thus, measurement of antibody avidity in addition to antibody concentrations may also serve as one of several parameters to establish non-inferiority.

It should be noted that the criteria discussed above are not meant to be all-inclusive in establishing non-inferiority. Additional immunological parameters will likely be discussed at

the February 26, 2001 workshop and may need to be considered when designing non-inferiority studies for pneumococcal conjugate vaccines. Any immunological parameter used to demonstrate non-inferiority will need to be measured in validated, standardized assays, capable of processing sufficient samples such that statistical criteria of non-inferiority can be met.

Clinical endpoint efficacy studies

Demonstration of preventive efficacy for clinical endpoints remains the gold standard to support licensure of vaccines. However, efficacy data based on clinical endpoints are likely to be difficult to obtain for future pneumococcal vaccines. As discussed, Prevnar™ was shown to be highly efficacious in a large trial for the primary endpoint of invasive disease. As a result, Prevnar™ is currently recommended for universal immunization of infants in the U.S. Therefore, if efficacy studies are to be required to obtain licensure for a new pneumococcal conjugate vaccine in the U.S., such studies would need to be designed as a) equivalence studies, using Prevnar™ in the comparator group, or b) controlled studies, using placebo or an unrelated control vaccine, in the comparator group, depending on the availability of Prevnar™ in the host country. If clinical efficacy were demonstrated for a new vaccine in either placebo-controlled or non-pneumococcal vaccine controlled studies, one might still question whether the new product were as effective as Prevnar™, unless the efficacy estimate were very high.

Some would argue that all pneumococcal vaccine studies should be conducted as comparative studies, using Prevnar™ in

the control group, regardless of the availability of Prevnar™ in the host country, based on ethical concerns ("World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects", 52nd WMA General Assembly, Edinburgh, Scotland, October 2000).

In order for efficacy trials conducted in foreign countries to be used in support of U.S. licensure of a new pneumococcal conjugate vaccine, immunological bridging to the U.S. population may be required. Age specific disease incidence and population differences in genetics, nutritional status, and background infections may affect the efficacy as well as the immune response induced by a particular vaccine. Thus, if efficacy is demonstrated in a non-U.S. population, immunological bridging to a U.S. population may be difficult in the absence of a correlate.

Studies demonstrating equivalent clinical endpoint efficacy for invasive disease would be substantially larger than placebo-controlled studies and, therefore, would likely require greater expenditure of resources. Large, simple trial designs might be able to provide essential efficacy data in an economically feasible manner, however, this concept has not been explored in detail. In order to more fully evaluate the regulatory options on which to base licensure of new pneumococcal vaccines, CBER biostatisticians have estimated sample sizes for comparative efficacy trials using equivalence trial designs (non-inferiority) under various assumptions of vaccine efficacy and pneumococcal disease rates, both for invasive disease and otitis media.

Future pneumococcal conjugate vaccines will likely contain more than 7 serotypes. In a comparative trial, it is plausible

that fewer cases of all pneumococcal disease would be observed in the group receiving an 11- or 13-valent vaccine, than in the Prevnar™ group, while serotype-specific efficacy might be superior in the Prevnar™ group. Therefore, the more appropriate endpoint for comparative efficacy studies might be disease caused by <u>any</u> pneumococcal serotype. Thus, in planning equivalence studies for invasive disease due to all pneumococcal serotypes, one might make assumptions for low and high prevalence areas to estimate samples sizes as shown in Tables 1 and 2 (see attachment II).

Available efficacy estimates for Prevnar™ in preventing otitis media due to serotype-specific pneumococcal disease are substantially lower than for invasive disease. The level of preventive efficacy supportive of an otitis media indication has not yet been determined by FDA. If the level of efficacy reported in the Finnish trial is deemed sufficient to support an otitis media indication, an indication for prevention of otitis media based on equivalency to Prevnar™, could be requested by manufacturers without prior demonstration of protection against invasive disease.

Efficacy studies based on otitis media endpoints would likely be conducted in a country like Finland, where tympanocentesis as therapy for acute otitis media is considered standard of care. Thus, in planning equivalence trials for the efficacy endpoint of otitis media due to all pneumococcal serotypes, one might make assumptions based on data from the Finnish otitis media trial of Prevnar™ in calculating sample sizes, as shown in Table 3 (see attachment II).

Recommending bodies (ACIP, AAP) may not be completely assured that vaccines licensed based on prevention of otitis media will be as effective as Prevnar™ in preventing invasive disease. However, neither does demonstration of non-inferiority of immune parameters provide that assurance, in the absence of a quantitative immune correlate for invasive disease. It can be argued that demonstration of prevention of otitis media is a more stringent test of vaccine efficacy than prevention of invasive disease; the relative efficacy estimates for Prevnar in preventing invasive disease and otitis media are consistent with that perspective.

Attachment I

DRAFT questions to the committee:

1. Would non-inferiority immune response trials comparing a new pneumococcal conjugate vaccine with Prevnar™ be sufficient for inferring efficacy against invasive disease for the new product? If so, what immunological parameter(s) should be used?

2. What criteria should be considered to evaluate serotypes not contained in Prevnar™?

3. For a new pneumococcal conjugate vaccine, can data demonstrating clinical efficacy against AOM (acute otitis media) also be used to infer efficacy against <u>invasive</u> pneumococcal disease?

4. An invasive disease efficacy study may be performed in a non U.S. population(s) with a new pneumococcal conjugate vaccine:

   a. If efficacy is demonstrated, would data derived from such a trial support licensure of the vaccine in the U.S.?

   b. If so, what are the immunologic criteria that should be used to establish comparability to Prevnar™ in U.S. bridging studies?

Attachment II

Table 1: Sample Size Estimates for Non-inferiority Comparative Invasive Disease Study in Low Prevalence Population, Prevnar vs. Vaccine X

Assumption: Invasive Disease Case Rate in Unvaccinated Population is 0.0015 (e.g., U.S. Children < 2 years of age)

Vaccine Efficacy Estimate		Acceptable Difference in Efficacy Between Prevnar™ and Vaccine X					
		10%		15%		20%	
	Case Rate Prevnar™ Group	Case Rate Vax X Group	N per group	Case Rate Vax X Group	N per group	Case Rate Vax X Group	N per group
0.70	0.00045	0.0006	247191	0.000675	109863	0.00075	61798
0.75	0.000375	0.000525	206008	0.0006	91560	0.000675	51502
0.80	0.0003	0.00045	164819	0.000525	73253	0.0006	41205
0.85	0.000225	0.000375	123624	0.00045	54944	0.000525	30906
0.90	0.00015	0.0003	82422	0.000375	36632	0.00045	20606

Table 2: Sample Size Estimates for Non-inferiority Comparative Invasive Disease Study in High Prevalence Population, Prevnar™ vs. Vaccine X

Assumption: Invasive Disease Case Rate in Unvaccinated Population is 0.005 (e.g., Native American Children < 2 years of age)

Vaccine Efficacy Estimate		Acceptable Difference in Efficacy Between Prevnar™ and Vaccine X					
		10%		15%		20%	
	Case Rate Prevnar™ Group	Case Rate Vax X Group	N per group	Case Rate Vax X Group	N per group	Case Rate Vax X Group	N per group
0.70	0.0015	0.002	74080	0.00225	32925	0.0025	18520
0.75	0.00125	0.00175	61749	0.002	27444	0.002	15438
0.80	0.001	0.0015	49411	0.00175	21961	0.00175	12353
0.85	0.00075	0.00125	37068	0.0015	16475	0.0015	9267
0.90	0.0005	0.001	24718	0.00125	10986	0.00125	6180

Sample size estimates will increase as the acceptable margin in vaccine efficacy between Prevnar™ and Vaccine X decreases, and with lower true efficacy of Prevnar™.

Table 3: Sample Size Estimates for Non-inferiority Comparative Otitis Media Study, Prevnar™ vs. Vaccine X

Assumption: Vaccine Efficacy Estimate for Prevention of Acute Otitis Media Case Due to All Pneumococcal Serotypes is 0.34 *

AOM Case Rate Unvaccinated Population (person yrs)*	Case Rate Prevnar™ Group	Acceptable Vaccine Efficacy For Vaccine X					
		0.30		0.275		0.25	
		Case Rate Vax X Group	N per group	Case Rate Vax X Group	N per group	Case Rate Vax X Group	N per group
0.40	0.26	0.28	5948	0.29	2644	0.30	1487
0.35	0.23	0.245	9733	0.25	3802	0.263	2011
0.30	0.20	0.21	19785	0.22	6107	0.225	3166

*Prevnar efficacy estimate and approximate case rates (inferred) from Eskola J, et als, 2001, NEJM 344: 403-8.

Sample size will increase as the background prevalence of acute otitis media due to pneumococcal serotypes decreases, and as the acceptable difference in efficacy compared to Prevnar™ narrows.