Group B Streptococcus
Maternal Immunization Program

Vaccines and Related Biological Products
Advisory Committee

May 17, 2018

Presentation Agenda

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Vice President, Chief Scientific Officer
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The Burden of GBS Disease
and Pfizer's GBS Vaccine

**Judith Absalon, MD, MPH**
Senior Medical Director
Pfizer Vaccine Research and Development

Potential GBS Vaccine
Clinical Development Pathways
Guidance on Approaches to Demonstrating Effectiveness of a Group B Streptococcal Conjugate Vaccine

- Pfizer is developing a six valent polysaccharide CRM$_{197}$ conjugate vaccine (GBS6) for the prevention of infant GBS invasive disease by maternal immunization.

- No regulatory precedent for the licensure of maternal vaccines and the development pathway for a GBS maternal vaccine will be complex.

- Pfizer is looking for guidance from CBER and the VRBPAC for acceptable approaches to demonstrate effectiveness to support future licensure of maternal GBS vaccines.

GBS Colonization Is a Risk Factor for GBS Disease

<table>
<thead>
<tr>
<th>GBS Recto-Vaginal Colonization</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates (%)</td>
<td>24.7</td>
</tr>
</tbody>
</table>

- Maternal GBS infections
- Stillbirth
- Preterm birth
- Infant invasive disease

### The Majority of Infant Invasive GBS Disease Occurs Within the First 90 Days of Life

<table>
<thead>
<tr>
<th></th>
<th>Pre-IAP in US (1990)</th>
<th>Post-IAP in US</th>
<th>South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOD (&lt;7 days)</td>
<td>1.82</td>
<td>0.21</td>
<td>1.41</td>
</tr>
<tr>
<td>LOD (≥7 days)</td>
<td>0.41</td>
<td>0.32</td>
<td>1.18</td>
</tr>
<tr>
<td>Total</td>
<td>0.53</td>
<td>0.53</td>
<td>2.59</td>
</tr>
</tbody>
</table>

EOD: early onset disease; LOD: late onset disease; IAP: Intrapartum Antibiotic Prophylaxis

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### Six Serotypes Cause >95% of Infant GBS Disease Globally


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Pre-clinical Proof of Principle: GBS6 Induced Maternal Antibodies Are Transferred and Protective

Maternal Protection with GBS6

PBS: Phosphate buffered saline; GBS6: Six valent polysaccharide CRM197 conjugate vaccine

All procedures performed on animals were in accordance with regulations and established guidelines, and were reviewed and approved by an Institutional Animal Care and Use Committee.

Pre-clinical Studies Confirm the Correlation Between Increased Maternal Antibody Levels and Protection

Protection Using Seropositive Human Sera

* Estimated maternal mouse concentration

All procedures performed on animals were in accordance with regulations and established guidelines, and were reviewed and approved by an Institutional Animal Care and Use Committee.
Anticapsular GBS IgG Antibody Concentrations are Linked to Protection

<table>
<thead>
<tr>
<th>Study1</th>
<th>Time period</th>
<th>Region</th>
<th>Study Size</th>
<th>Case1</th>
<th>Threshold (Reduced Disease Risk Based on Bayesian Model)</th>
<th>Case1</th>
<th>Threshold (Reduced Disease Risk Based on Bayesian Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker 2014</td>
<td>EOD</td>
<td>US</td>
<td>132,000</td>
<td>17</td>
<td>2 µg/mL (51%)</td>
<td>9</td>
<td>1 µg/mL (100%)</td>
</tr>
<tr>
<td>Dangor 2015</td>
<td>30 Days</td>
<td>S. Africa</td>
<td>45,000</td>
<td>27</td>
<td>5 µg/mL (85%)</td>
<td>29</td>
<td>3 µg/mL (98%)</td>
</tr>
<tr>
<td>Fabbrini 2016</td>
<td>EOD</td>
<td>Europe</td>
<td>25,000</td>
<td>8</td>
<td>1 µg/mL (81%)</td>
<td>23</td>
<td>1 µg/mL (78%)</td>
</tr>
</tbody>
</table>

- Differences between these studies prevent absolute comparison
- Standardized assays are being developed to provide a link between sero-epidemiology studies and vaccines in development


With Maternal Immunization, Higher GBS CPS Antibody Titers Increase the Proportion of Infants Protected

- Naturally-Acquired Maternal Ab Titer
- Minimum Protective Threshold Titer

CC-9
With Maternal Immunization, Higher GBS CPS Antibody Titers Increase the Proportion of Infants Protected

Potential GBS Vaccine Clinical Development Pathways

Judith Absalon, MD, MPH
Senior Medical Director
Pfizer Vaccine Research and Development
Clinical Development of a Group B Streptococcal Conjugate Vaccine

- Pfizer is developing a 6-valent polysaccharide CRM$_{197}$ conjugate vaccine (GBS6) for the prevention of infant invasive GBS disease by maternal immunization
  - First in human clinical studies initiated June 2017
  - Studies in pregnant women planned in late 2018

- Different clinical development pathways can be pursued to demonstrate effectiveness to support vaccine licensure

Potential GBS Clinical Development Pathways: Traditional or Accelerated Approval

<table>
<thead>
<tr>
<th>Initial Basis for Licensure</th>
<th>Endpoint(s)</th>
<th>Regulatory Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness established with a disease endpoint study</td>
<td>Incidence of infant invasive GBS disease</td>
<td>Traditional approval</td>
</tr>
<tr>
<td>Effectiveness demonstrated using an established correlate of protection$^1$</td>
<td>Proportion of infants achieving protective antibody levels</td>
<td>Traditional approval</td>
</tr>
<tr>
<td>Effectiveness demonstrated initially with a surrogate of protection$^2$</td>
<td>Proportion of infants achieving protective antibody levels</td>
<td>Accelerated approval</td>
</tr>
</tbody>
</table>

1. Correlate of protection is generally a laboratory parameter that has been shown from adequate and well-controlled trials to be associated with protection from clinical disease. FDA Guidance on Combination Vaccines 1997.
2. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Drug companies are still required to conduct studies to confirm the anticipated clinical benefit. FDA 1992 Accelerated Approval Program.
Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- Demonstrate effectiveness in clinical efficacy trial with disease endpoint
- Demonstrate effectiveness using an established immunological correlate of protection
- Demonstrate effectiveness using a surrogate of protection and clinical disease endpoint

An Efficacy Study In the US is Not Feasible

<table>
<thead>
<tr>
<th>Disease Rate (Per 1000 Live Births)</th>
<th>Evaluable Pregnant Women (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>600,000</td>
</tr>
<tr>
<td>1.0</td>
<td>500,000</td>
</tr>
<tr>
<td>2.0</td>
<td>400,000</td>
</tr>
<tr>
<td>3.0</td>
<td>300,000</td>
</tr>
<tr>
<td>3.5</td>
<td>200,000</td>
</tr>
</tbody>
</table>

LB: 95% lower bound confidence level.
Efficacy Trial Size Could Be Reduced if Conducted in Higher Incidence Countries

Total sample size required to demonstrate vaccine efficacy (VE)
(90% Power, 1:1 Randomization, 5% Type I Error)

- LB=20% and Assumed VE=70%
- LB=0% and Assumed VE=70%

LB: 95% lower bound confidence level.


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Efficacy Trial Size Could Be Reduced if Conducted in Higher Incidence Countries or if a Smaller Lower Bound Confidence Interval Is Used

LB: 95% lower bound confidence level.

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Could a Composite Clinical Endpoint Facilitate a More Rapid Assessment of Vaccine Efficacy?

- Infant Invasive GBS Disease
- Preterm birth
- Maternal Invasive GBS Disease

- Limited data
- Multifactorial etiology
- Early preterm births would not be evaluable

- May dilute ability to detect vaccine effect due to lack of GBS specificity

- Burden of maternal invasive GBS disease not well established in LMICs
- Impact on efficacy trial contingent on incidence and relationship to infant invasive GBS disease

Vaccine Efficacy Trials Can Be Large

GBS Vaccine Efficacy (N~50,000)

Pregnant Women
Maternal GBS Vaccine Efficacy Trials Will Be Both Large and Complex

- This study would take more than 8 years to enroll with approximately 100 experienced sites in high GBS incidence regions
  - A GBS vaccine would therefore not be available for at least 12 years from initiation of a clinical efficacy trial

Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- Demonstrate effectiveness in clinical efficacy trial with disease endpoint
- Demonstrate effectiveness using an established immunological correlate of protection
- Demonstrate effectiveness using a surrogate of protection and clinical disease endpoint
Precedent Established for Immunological Correlates of Protection for Encapsulated Pathogens

A
Natural History Seroepidemiology Evidence

B
Disease Endpoint Trial

C
Immunological Endpoint Trial

- Haemophilus influenzae type B
- Neisseria meningitidis serogroups
- Streptococcus pneumoniae serotypes
- GBS

Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- Demonstrate effectiveness in clinical efficacy trial with disease endpoint
- Demonstrate effectiveness using an established immunological correlate of protection
- Demonstrate effectiveness using a surrogate of protection and clinical disease endpoint
A Combined Immunological and Clinical Disease Endpoint Pathway Could Result in Earlier Licensure

Potential GBS Vaccine Clinical Development Pathways to Demonstrate Vaccine Effectiveness

- There is an important unmet medical need for a vaccine to prevent GBS disease in infants
- The mechanism of action for immune protection is established
- Low incidence rates mean that clinical endpoint efficacy studies alone will take many years and may not be practical
- Pfizer is looking forward to working with the FDA to develop approaches that may bring a safe and effective vaccine to licensure