

5. Human safety data

- Individual active components
 - Controlled studies
 - Partially controlled or uncontrolled studies
 - Documented case reports
 - Pertinent marketing experiences that may influence a determination as to the safety of each individual active component
 - Pertinent medical and scientific literature
- Combinations of the individual active components
 - Controlled studies
 - Partially controlled or uncontrolled studies
 - Documented case reports
 - Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components
 - Pertinent medical and scientific literature
- Finished biological product
 - Controlled studies
 - Partially controlled or uncontrolled studies
 - Documented case reports
 - Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product
 - Pertinent medical and scientific literature

6. Efficacy data

- Individual active components
 - Controlled studies
 - Partially controlled or uncontrolled studies
 - Documented case reports
 - Pertinent marketing experiences that may influence a determination as to the efficacy of each individual active component
 - Pertinent medical and scientific literature
- Combinations of the individual active components
 - Controlled studies
 - Partially controlled or uncontrolled studies
 - Documented case reports
 - Pertinent marketing experiences that may influence a determination as to the effectiveness

of combinations of the individual active components

- Pertinent medical and scientific literature
- Finished biological product
 - Controlled studies
 - Partially controlled or uncontrolled studies
 - Documented case reports
 - Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product
 - Pertinent medical and scientific literature

7. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.

8. If the submission is by a licensee, a statement signed by the responsible head (as defined in §600.10 of this chapter) of the licensee shall be included, stating that to the best of his knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature.

If the submission is by an interested person other than a licensee, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the information, favorable and unfavorable, available to him pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

SOURCE, 21 CFR 601.25

Appendix 3.5

TYPES OF STUDIES BOB USED TO EVALUATE THE SAFETY AND EFFICACY OF POLYVALENT PNEUMOCOCCAL VACCINE

Epidemiologic Studies

In 13 of the 26 studies on which BOB based its evaluation of the new polyvalent pneumococcal vaccine, investigators attempted to determine the distribution of pneumococcal serotypes among U.S. and

foreign study subjects with pneumococcal disease.¹

¹ Investigators in other epidemiologic studies, most notably Robert Austrian in a study funded by NIAID, surveyed the distribution of pneumococcal serotypes in the United States (Austrian, 1978), but the extent to which BOB relied on data from other investigations was not assessed in this report.

These 13 studies, most of which were sponsored by the U.S. Government (e. g., the National Institute of Allergy and Infectious Diseases (NIAID)) or academic institutions, involved about 13,000 cases of pneumococcal disease; one U.S. study alone involved 12,000 cases.

Determining the types of pneumococci that produce pneumococcal pneumonia is a difficult task for at least two reasons. First, there is no simple, inexpensive, and reliably accurate diagnostic technique that can be used to isolate and identify specific types of pneumococci in the lungs of persons with pneumococcal pneumonia. Second, in few, if any, epidemiologic studies are data collected in a manner that permits investigators to calculate for a defined population the rate of occurrence of new cases of pneumococcal pneumonia, i.e., the pneumococcal pneumonia incidence rate.

The problem in ascertaining which type of pneumococcus produces a given case of pneumonia is this: The most reliable diagnostic technique, which involves extracting pneumococci from the lung (trans-tracheal aspiration), is a difficult, expensive, and potentially harmful procedure; alternative techniques, though, have serious limitations and usually do not yield reliably accurate results. The latter include examining cultures of throat and sputum samples (simple and inexpensive, but itself an inaccurate indication of infection in the lungs), examining cultures of blood samples (simple, inexpensive, and accurate, but only when, as occurs in about 25 percent of pneumococcal pneumonia cases, a person has bacteremia), and assaying of antibodies in blood (dependent on skilled personnel and specific technology, expensive, and accurate only when a person has bacteremia).

If a reliable, accurate, inexpensive, and safe diagnostic technique for isolating pneumococci from the lungs of persons with pneumococcal pneumonia were available, epidemiologic studies to determine incidence rates of diseases produced by each type of pneumococcus could be conducted more easily and more accurately than they can be at present. A population could be defined (e. g., by age, geographical location, or disease state) and monitored for pneumococcal disease for a specified time period. Then the number of cases of pneumonia (or other types of pneumococcal infection) among the defined population caused by each of the 83 types of pneumococci could be determined. Annual incidence rates for diseases caused by each type of pneumococcus subsequently could be tabulated as follows:

Type of pneumococcus	Incidence rate of pneumococcal pneumonia
Type 1	X cases per 100,000 persons per year
Type 8	Y cases per 100,000 persons per year

To date, thorough epidemiologic investigations to determine the incidence of pneumococcal pneumonia in the United States have not been conducted on a national basis. Furthermore, in some studies conducted at present, researchers do not identify or describe the base population from which they have extracted pneumonia cases and pneumococcal types. Pneumococcal pneumonia incidence rates, therefore, especially among specified populations such as the elderly, have not been possible to calculate.

Partly because of the low rates of occurrence of pneumococcal diseases in this country, U.S. epidemiologic studies of these diseases consist primarily of investigations of case reports. Such case reports are generated by investigators who select one of the diagnostic techniques described above, and identify and record the types of pneumococci they isolate from a selected group of pneumonia patients. Data from various epidemiologic studies are often not comparable. Because diagnostic techniques used to isolate and identify pneumococcal types vary dramatically, each study produces case reports based on different assumptions.

Notwithstanding these problems, BOB used epidemiologic studies as a basis for its decision, made jointly with the manufacturer, regarding the formulation of the currently licensed 14-valent pneumococcal vaccine. This formulation was based primarily on results from epidemiologic studies in which blood cultures of pneumococci and serum assays of pneumococcal antibodies were used to determine which types of pneumococci were present in patients with pneumococcal bacteremia and pneumonia.

Immunogenicity Studies

The immunogenicity of experimental pneumococcal vaccines was evaluated in 20 of the 26 studies on which BOB based its evaluation. Thirteen of the studies, were sponsored by industry, mostly by Merck Sharp and Dohme, and these studies involved about 4,000 subjects in foreign countries. In a study sponsored by NIAID, Austrian measured antibody responses in another 4,000 subjects in the United States.

Immunogenicity studies were conducted for each serotype of antigen in the 14-valent vaccine. The purpose of these studies was to ascertain the level of protective antibody production that was induced in persons receiving polyvalent polysaccharide pneumococcal vaccine. Overall, the vaccine produced a good antibody response in most subjects except those under 2 years of age.²

²Apparently, children under 2 years old have not yet fully developed an immune system that reacts sufficiently to polysaccharide antigens to produce consistently good antibody titers.