

FDA Briefing Document

Vaccines and Related Biological Products Advisory Committee Meeting

November 7, 2017

**Clinical Development Plan for Pfizer's Investigational *Staphylococcus aureus*
Vaccine (SA4Ag) Intended for Pre-Surgical Prophylaxis in Elective Orthopedic
Surgical Populations**

I. INTRODUCTION

1.1 *Staphylococcus aureus* Infections

Staphylococcus aureus is a Gram-positive bacterium that exists both as a commensal and as an important human pathogen.^{1,2} *S. aureus* is responsible for a broad range of clinical manifestations ranging from skin and soft tissue infections to life-threatening invasive infections. It is a leading cause of bacteremia and infective endocarditis, as well as osteoarticular, pleuropulmonary, and device-related infections.² *S. aureus* infections can result in substantial morbidity and mortality.³

Infections are initiated when a breach of the skin or mucosal barrier allows staphylococci access to adjoining tissues or the bloodstream.⁴ Approximately 30% of the human population is colonized with *S. aureus*.^{2,5} The bacterium's primary niche in humans is the anterior nares, but the skin, throat, gastrointestinal tract, and female urogenital tract are secondary niches.³⁻⁵ *S. aureus* nasal carriage is a well-recognized risk factor of infection due to this bacterium, especially in hospitalized patients.³ Whether an infection is contained or spreads depends on a complex interplay between *S. aureus*' diverse array of immune evasion determinants and host defense mechanisms.⁴⁻⁷ Populations at high risk of invasive *S. aureus* disease include surgical patients, individuals with foreign body implants, low-birth-weight neonates, patients with indwelling catheters and endotracheal intubation, patients on immunosuppressive or cancer therapy, diabetics, end-stage renal disease (ESRD) patients, and nursing home residents.⁸

The innate adaptability of *S. aureus* has led to the emergence of resistance to multiple classes of antibiotics through acquisition of mobile genetic elements encoding resistance determinants or mutations in loci influencing antibiotic sensitivity.⁵ Methicillin-resistant *S. aureus* (MRSA) was first described shortly after the introduction of methicillin in 1961, but it was uncommon outside of the healthcare environment until the 1990s.⁹⁻¹¹ With the spread of MRSA outside of hospitals, invasive infections due to *S. aureus* have been frequently reported in previously healthy individuals in the community.³ MRSA is now classified as either community-associated (CA-MRSA) or healthcare-associated MRSA (HA-MRSA).¹¹ The two MRSA subclasses, which are genetically distinct, differ in pathogenicity, virulence, antibiotic resistance profile, and population affected. CA-MRSA isolates contain a novel cassette element (SCC 4) and exotoxin (Panton-Valentine leucocidin).^{11,12} They are typically susceptible to many non-beta lactam antibiotics, affect young, otherwise healthy people, and predominantly affect the skin and lungs. Meanwhile, HA-MRSA isolates contain SCC types 1 to 3, are typically multiple-drug resistant, affect recently hospitalized patients, hemodialysis patients, HIV-infected patients, institutional residents, and the elderly and affect a variety of areas of the body.¹¹ It is estimated that ~2% of the population is colonized with MRSA.¹³

The USA300 strain of *S. aureus* has been noted to spread rapidly in the U.S.¹ Although initially described as community-associated MRSA, this strain is now common in healthcare settings and is replacing other strains of MRSA as a cause of healthcare-associated infections (HAIs).¹

According to the Centers for Disease Control and Prevention (CDC), the incidence rate of health-care associated invasive MRSA infections declined steadily from 27.1 infections per 100,000 population in 2008 to 18.7 infections per 100,000 population in 2012.¹⁴ Despite downward trends in rates of invasive MRSA infection, a large burden of disease remains, particularly among recently discharged patients, older populations, and long term care residents.¹⁵

S. aureus Surgical Site Infections

While advances have been made in infection control practices, SSIs remain a substantial cause of morbidity, prolonged hospitalization and death.¹⁶ They are the second most common cause of HAIs in the U.S. (following catheter-associated urinary tract infections, which are predominantly caused by Gram negative bacteria).¹⁷ SSIs are associated with a mortality rate of 3%, and 75% of SSI-associated deaths are directly attributable to the SSI.¹⁶

Based on data reported to CDC's National Healthcare Safety Network (NHSN) for HAIs that occurred between 2011 and 2014, a total of 365,490 HAIs were reported from 4,515 healthcare facilities in the U.S.¹⁷ This period coincides with increased use of NHSN due to new HAI reporting requirements for participation in CMS Quality Reporting Programs.¹⁷ The NHSN system monitors selected surgical procedures for SSIs at participating institutions, and these SSIs accounted for 36.4% of HAIs reported to the system (133,080 infections).¹⁷ Broken down by the type of surgery, SSIs were most frequently reported following abdominal surgery (63,508) followed by orthopedic (31,539), ob/gyn (22,231), and cardiac (10,439) surgeries.¹⁷ Overall, *S. aureus* was the most prevalent pathogen isolated from SSIs (20.7%) followed by *E. coli* (13.7%). *S. aureus* was also the most prevalent pathogen isolated from all surgical types except abdominal surgery and transplant surgery.¹⁷ In descending order, *S. aureus* accounted for 44.2% of orthopedic SSIs, 39.0% of breast SSIs, 30.4% of cardiac SSIs, 31.2% of neurological SSIs, 29.5% of prostate SSIs, 26.9% of vascular SSIs, and 8.7-17.7% of ob/gyn, neck, abdominal and transplant SSIs.¹⁷ The proportion of SSI-causing *S. aureus* isolates that were resistant to oxacillin/methicillin/cefoxitin was steady at approximately 43-45%.¹⁷

Complex surgical procedures with implanted foreign material have higher rates of post-operative infections compared to procedures without implanted foreign material.^{18,19} Prosthetic implantation was demonstrated in animal models of *S. aureus* infection to reduce the inoculum required to cause infection by 100,000-fold.^{2 2}

S. aureus is capable of growing as a biofilm, which it forms on the surface of implants.¹¹ The bacteria adhere to the implant, become sessile, reduce their metabolic rate, and secrete a glycalyx

layer which protects them from antibiotics, phagocytosis, and opsonization.^{11,20} Treatment of infections in the presence of a prosthetic implant may also be more difficult due to a lack of vascularization in the bone/implant interface.² Biofilm-associated infections prolong the length of hospitalization, result in additional surgical revisions and extend rehabilitation after discharge.^{21,22}

SSIs can be categorized into superficial incisional SSIs, deep incisional SSIs, and organ/space SSIs. The CDC criteria for each category are as follows:¹⁶

- Superficial incisional SSI: infection occurs within 30 days after any operative procedure, involves only skin and subcutaneous tissue of the incision, and the patient has at least one of the following:
 - purulent drainage,
 - organism identified from aseptically-obtained specimen,
 - the superficial incision is deliberately opened by a surgeon, attending physician or designee and testing to identify the bacterium are not performed, and the patient has at least one of the following signs or symptoms: pain or tenderness, localized swelling, erythema or heat; or
 - diagnosis of a superficial incisional SSI by the surgeon, attending physician or designee.

- Deep incisional SSI: infection occurs within 30 to 90 days after the operative procedure, involves deep soft tissues of the incision (e.g., fascial and muscle layers), and the patient has at least one of the following:
 - Purulent drainage
 - Deep incision spontaneously dehisces, or is deliberately opened or aspirated by a surgeon or attending physician or other designee and organism is identified for the purposes of clinical diagnosis or treatment or microbiologic testing is not performed, and the patient has at least one of the following signs or symptoms: fever ($> 38^{\circ}\text{C}$), localized pain or tenderness. A microbiologic test that has a negative finding does not meet this criterion.
 - An abscess or other evidence of infection involving the deep incision detected on gross anatomical or histopathologic exam, or imaging test.

- Organ/Space SSI: infection occurs within 30 to 90 days after the operative procedure and infection involves any part of the body deeper than the fascial/muscle layers that is

opened or manipulated during the operative procedure, and the patient has at least one of the following:

- Purulent drainage from a drain placed into the organ/space
- Organisms identified from an aseptically-obtained fluid or tissue in the organ/space by microbiologic testing performed for the purposes of clinical diagnosis or treatment
- An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection, and meets at least one criterion for a specific organ/space infection site listed in Table 3 of CDC's SSI Procedure Associated Module.

1.2 Prevention

Prevention of *S. aureus* infections relies on implementation of adequate principles of infection control²³ (e.g., hand hygiene, contact precautions, and environmental control).²⁴

CDC's guideline for the prevention of SSIs recommends that patients should shower or bathe with soap (antimicrobial or nonantimicrobial) or an antiseptic agent on at least the night before the operative day.²⁵ Skin preparation in the operating room should be performed using an alcohol-based agent unless contraindicated.²⁵ During surgery, glycemic control should be implemented using blood glucose target levels less than 200 mg/dL, and normothermia should be maintained in all patients.²⁵ Increased fraction of inspired oxygen should be administered during surgery and after extubation in the immediate postoperative period for patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation.²⁵ Antimicrobial prophylaxis should be administered when indicated based on published clinical practice guidelines and times such that a bactericidal concentration of the agents is established in the serum and tissues when the incision is made.²⁵

A joint clinical practice guideline for antimicrobial prophylaxis in surgery recommends no antibiotic prophylaxis for the following types of surgeries: 1) clean orthopedic procedures involving the hand, knee, or foot and not involving implantation of foreign materials, 2) elective, low risk laparoscopic procedures, and 3) clean head and neck procedures.²⁶ Antimicrobial prophylaxis is recommended for all other surgical procedures (with and without implantation of foreign material).²⁶

Decolonization of MRSA carriers is a common and widely implemented component of infection control strategies; however, decolonization success rates vary substantially, ranging from 23% to 96%.²⁷ A decision regarding whether to implement global *S. aureus* screening and decolonization protocols should depend on baseline SSI and MRSA rates.²⁸ Screening and nasal

mupirocin decolonization is recommended for MRSA *S. aureus*-colonized patients prior to total joint replacement and cardiac procedures.^{26,28}

1.3 Treatment

The emergence of multi-drug resistant *S. aureus* strains has made the treatment of *S. aureus* infections challenging. There are relatively few antibiotic agents available to treat MRSA infections.⁹ Vancomycin has been the mainstay of parenteral therapy for MRSA infections.²⁴ However, experts have expressed concerns about the use of vancomycin due to its slow bactericidal activity, the emergence of resistant strains, and possible “MIC creep” among susceptible strains.²⁴

With the antibiotic pressure exerted by the increasing use of vancomycin to treat MRSA infections, vancomycin-resistant *S. aureus* (VRSA) isolates have been reported in the United States.⁹ Vancomycin-intermediate *S. aureus* (VISA) strains, first reported in Japan in 1996, have been identified more commonly in many countries, including the United States.⁹ In addition, there has been an observation of a slow but steady increase in the level of resistance to vancomycin among unselected *S. aureus* strains that can occur with vancomycin therapy.⁹

Treatment recommendations for mild purulent *S. aureus* infections (e.g., furuncle, carbuncle, and abscess) include incision and drainage.²⁹ Recommendations for treatment of moderate (systemic signs of infection) to severe (e.g., failed incision and drainage + oral antibiotics) purulent *S. aureus* infections include incision and drainage, culture and sensitivity, and empiric followed by defined antimicrobial therapy.²⁹ Treatment of nonpurulent *S. aureus* infections (e.g., necrotizing infection, cellulitis) includes oral antibiotics for mild cases, intravenous antibiotics for moderate cases, and emergent surgical inspection and debridement plus empiric antibiotic therapy for severe cases.²⁹

Treatment of implant-associated SSIs is usually accomplished by one or more operative debridement procedures, combined with prolonged intravenous antibiotics to eradicate or control the infection.^{11,30} When indicated and feasible, the implant is removed or exchanged.^{11,30}

II. CLINICAL DEVELOPMENT OF *STAPHYLOCOCCUS AUREUS* VACCINES TO DATE

Compared to other bacterial pathogens, *S. aureus* presents several unique challenges in the development of an effective vaccine. *S. aureus* has a broad scope, frequency and range of virulence factors compared to other common pathogens.³¹ As part of the normal human flora (e.g. not a transient colonizer like *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*) of about 30% of healthy humans,^{2,5,26} it has successfully adapted to achieve stable colonization in the

immunocompetent host.³¹ Protective immunity against *S. aureus* is not completely understood.³¹ In contrast to some vaccines against other pathogens, animal models (especially murine models) have not predicted success in humans.³¹

The two most extensively tested investigational vaccines to date, described below, did not meet pre-specified primary efficacy endpoints in their respective Phase 3 clinical trials for the prevention of invasive *S. aureus* disease in adult populations with high rates of *S. aureus* infection.³²

2.1 Investigational Bivalent *S. aureus* Glycoconjugate Vaccine, “StaphVAX”¹

“StaphVAX” was an investigational bivalent conjugate vaccine developed by Nabi Biopharmaceuticals. It was formulated to contain 100 µg each of capsular polysaccharide types 5 and 8 conjugated to recombinant pseudomonal exoprotein A (a carrier protein).³³ Although the vaccine showed some promise in an initial Phase 3 trial in ESRD patients on hemodialysis, it was found to be ineffective in a second Phase 3 trial, leading to its development being halted.³⁴

The initial randomized, double-blinded, placebo-controlled Phase 3 trial evaluated “StaphVAX” efficacy against *S. aureus* bacteremia in adults aged 18 years or older with ESRD and on hemodialysis. A total of 1804 subjects were randomized at a 1:1 ratio to receive either one injection of “StaphVAX” or phosphate buffered saline. Patients were stratified by their nasopharyngeal carriage of *S. aureus* and dialysis access (native-vessel fistula versus synthetic or heterologous graft). The primary endpoint was prospectively defined as the incidence of *S. aureus* bacteremia in the year following vaccination.³³

The efficacy of “StaphVAX” at 1 year was 26% (reduction in bacteremia) compared to placebo and was not statistically significant ($P = 0.228$). In a post-hoc analysis, evaluating the performance of the vaccine through various earlier time points, “StaphVAX” was shown to reduce *S. aureus* bacteremia by 64% through 32 weeks of follow-up ($P = 0.02$) and by 57% through 40 weeks of follow-up ($P = 0.02$). When antibody levels were analyzed for a potential correlation with efficacy, it appeared that protection declined when geometric mean antibody levels in the population fell below approximately 80 µg/ml.^{33,35}

Based on the post-hoc analyses, Nabi conducted a second randomized, placebo-controlled, double-blind Phase 3 clinical trial in 3,359 patients with ESRD on hemodialysis.³⁶ Two doses of “StaphVAX” were administered at weeks 0 and 35. The primary endpoint was prospectively defined as the incidence of *S. aureus* bacteremia at 35 weeks following the first dose of the vaccine.³⁶ This second “StaphVAX” trial also failed to demonstrate a protective effect of the vaccine on the primary endpoint.³⁶ Safety analyses revealed no significant differences in rates of

¹ StaphVAX was the proprietary name proposed by Nabi Biopharmaceuticals.

SAEs or deaths between vaccine and placebo groups.³⁶

2.2 Investigational V710 Vaccine

Merck Sharp & Dohme Corp developed V710, a *S. aureus* vaccine containing *S. aureus* 0657nI iron surface determinate B (IsdB).³⁷ A randomized (1:1), double-blind, placebo-controlled (0.9% saline placebo), multicenter Phase 3 trial was conducted internationally with V710 to evaluate the safety and efficacy of a single dose of V710 (60 µg) when administered to adults 18 years of age or older scheduled for cardiothoracic surgery involving a full median sternotomy.³⁷ The primary objective was to determine if V710, when administered between 14 and 60 days prior to full median sternotomy, resulted in a reduction in the proportion of adults with postoperative *S. aureus* bacteremia and/or *S. aureus* deep sternal wound infections through postoperative day 90 by at least 20% relative to placebo.³⁷

The trial was event-driven. A group-sequential design with 4 distinct stages (at 24, 48, 77 and 107 primary endpoint events) was used such that after each threshold of primary endpoint events was reached, an analysis of futility and/or efficacy was conducted.³⁷

Following a review of the second interim analysis, the data monitoring committee recommended suspension of enrollment and vaccination because of concerns about a possibly higher rate of mortality and multiorgan failure in V710 vaccine recipients than in placebo recipients.³⁷

Following review of supplemental results, the data monitoring committee recommended permanently closing the study to enrollment because of continuing safety concerns coupled with a low probability of success. The Sponsor followed the recommendations from the data monitoring committee.³⁷

After locking the database, 7,983 subjects had been vaccinated. In the primary modified ITT analysis, V710 vaccine was not significantly more efficacious than placebo in preventing the prespecified combined endpoint; there were 22 adjudicated cases in 3528 evaluable V710 recipients vs 27 adjudicated cases in 3517 evaluable placebo recipients, yielding a relative risk of 0.81 (95% CI 0.44 – 1.48). Vaccine efficacy was calculated as 18.5% (95% CI -48.6%, 55.8%). No significant differences in efficacy between the vaccine and placebo groups were observed at any point in the study.³⁷

In safety analyses, significantly more subjects experiencing a primary endpoint (*S. aureus* bacteremia and/or *S. aureus* deep sternal wound infection) died in the V710 group (7 deaths) than in the placebo group (2 deaths), yielding respective mortality rates of 35.7 (95% CI 14.4, 73.6) and 7.8 (95% CI 0.9, 28.1) per 100 person-years (difference 28.0 (95% CI 2.0, 66.7) per 100 person-years). Similar findings were observed among subjects with any postoperative *S. aureus* infection (15 deaths in the V710 vaccine group versus 4 deaths in the placebo group, yielding a difference in mortality rates of 18.8 (95% CI 8.0, 34.1) per 100 person-years). Among

subjects experiencing a primary endpoint, 3 subjects in the V710 group and 0 subjects in the placebo group died with multiorgan failure, yielding respective mortality rates of 14.9 (95% CI 3.1, 43.4) and 0.0 (0.0, 14.2) per 100 person-years (difference 14.9 (95% CI 0.0, 43.7) per 100 person-years.³⁷

Since the protocol contained no pre-specified criteria for multiorgan failure, the adverse event term could have been applied inconsistently at different study sites. Despite the post hoc nature of the exploratory analyses, the consistency of the association between V710 and later development of multiorgan failure across multiple subgroups raised the possibility that the relationship may not be the result of chance alone.³⁷

In a series of post hoc subgroup analyses, vaccine efficacy was numerically higher against MSSA than MRSA infections, against superficial than deep surgical site infections, and in baseline nasal *S. aureus* carriers than in noncarriers, but the wide confidence intervals around these point estimates included zero.³⁷

Anti-IsdB IgG titers in V710 recipients who developed primary *S. aureus* infections were comparable with the titers achieved in V710 recipients who did not develop *S. aureus* infection. V710 induced a significant, although modest and transient, increase in functional antibodies that could facilitate the uptake of *S. aureus* into neutrophils.³⁷

III. PFIZER'S INVESTIGATIONAL SA4AG VACCINE

Pfizer has developed an investigational *S. aureus* 4-antigen vaccine (SA4Ag), which is currently in Phase 2 clinical development. SA4Ag contains the following 4 surface-expressed *S. aureus* antigens:

- *S. aureus* capsular polysaccharide serotype 5 (CP5) and serotype 8 (CP8), each conjugated to the nontoxic mutant form of diphtheria toxin cross-reactive material 197 (CRM₁₉₇).
- a recombinant form of *S. aureus* clumping factor A. ClfA is responsible for bacterial adhesion to fibrinogen.
- a recombinant form of *S. aureus* manganese transporter C (MntC) protein. *S. aureus* require trace elements such as manganese for growth.³⁸

Pfizer selected these four antigens in order to target the following three bacterial virulence mechanisms: 1) evasion of opsonophagocytosis via polysaccharide capsule expression (CP5, CP8), 2) binding to host fibrinogen (ClfA), and 3) sequestering essential manganese (MntC). Pfizer also indicates that these antigens were selected because they are well-conserved antigens that are expressed during early infection. Pfizer intends for this vaccine to be broadly protective across the range of clinical isolates of *S. aureus* regardless of antibiotic resistance profile.

Phase 1/2 studies in adults 18 through 85 years of age used assays to assess, either directly or indirectly, the capacity of the vaccine to induce a functional antibody response against each vaccine antigen. In these studies, the SA4Ag safety profile has been unremarkable.^{39,40} In July 2015, Pfizer initiated a large, randomized, double-blind, placebo-controlled clinical endpoint study (study B3451002) evaluating the safety and efficacy of a single intramuscular dose of SA4Ag in preventing post-operative invasive *S. aureus* disease in adults ≥ 18 through 85 years of age scheduled to undergo elective open, posterior approach, multilevel, instrumented, spinal fusion surgery. Instrumented procedures involve implantation of prosthetic material (e.g., rods, screws, plates, hooks, wires and/or bone cages). For this study, spinal fusion may involve the cervical, thoracic, lumbar, or sacral vertebrae or the pelvis. Eligible subjects are randomized at a 1:1 ratio to receive either a single dose of SA4Ag or placebo (excipients of SA4Ag formulation) 10 to 60 days prior to undergoing the index surgical procedure. The study is event driven. The pre-specified primary endpoint is defined as *S. aureus* bloodstream infections and/or deep incisional or organ/space SSIs occurring within 90 days of the index surgical procedure, as confirmed by an event adjudication committee. The study is designed to have 88% power to demonstrate vaccine efficacy with a 95% LB CI of $>20\%$, if the placebo infection rate is 1.4% for the primary outcome and the true vaccine efficacy is $\geq 70\%$. Secondary endpoints include 1) primary endpoint cases occurring within 180 days of the index surgical procedure, 2) *S. aureus* SSIs occurring within 90 days of the index surgical procedure, and 3) *S. aureus* SSIs occurring within 180 days of the index surgical procedure. Exploratory endpoints include 1) invasive *S. aureus* disease occurring within 90 days of the index surgical procedure, 2) invasive *S. aureus* disease occurring within 180 days of the index surgical procedure, 3) efficacy based on baseline *S. aureus* colonization status, and 4) *S. aureus* colonization before and after SA4Ag administration. Invasive *S. aureus* disease is defined as culture of *S. aureus* from a normally sterile location, with clinical evidence of disease. Subjects will be followed for safety through day 180 after the index surgery. The study includes prospective criteria to identify multiple organ failure after vaccination and surgery.

Pfizer's clinical development plan is intended to support traditional approval for the following initial indication: "active immunization for the prevention of invasive postoperative disease caused by *Staphylococcus aureus* in adults 18 years of age and older who are undergoing elective orthopedic surgery." Pfizer intends to use safety and efficacy data from study B3451002 (conducted in instrumented, posterior-approach, multilevel spinal fusion surgical patients) as the primary data supporting this proposed indication. Pfizer's rationale for this clinical development plan is that the study population enrolled in study B3451002 is representative of other elective orthopedic surgical populations. The evidence supporting this assertion is discussed in section IV, below.

Pfizer therefore proposes that it is scientifically valid to assume that if SA4Ag is safe,

immunogenic, and effective in adults undergoing elective, posterior-approach, instrumented, multilevel spinal fusion surgery in study B3451002, then the vaccine will be comparably safe and effective in adults undergoing other elective orthopedic surgeries.

IV. PFIZER'S RATIONALE FOR THE PROPOSED CLINICAL DEVELOPMENT PLAN

Pfizer states that their clinical development plan for SA4Ag initially targets an invasive *S. aureus* disease indication in adults undergoing elective orthopedic surgery for the following reasons:

- 1) invasive post-operative *S. aureus* infections in adults who have undergone elective orthopedic surgery represent an unmet medical need that carries a significant burden with high morbidity and mortality risk for patients;
- 2) an elective orthopedic surgery population is generally healthy, immune competent, and has low postoperative morbidity and mortality in the absence of infection; and
- 3) elective orthopedic surgeries are typically scheduled sufficiently in advance to permit preoperative vaccination.

In the absence of an established correlate of protective immunity against invasive *S. aureus* disease, a clinical endpoint trial is required to demonstrate the efficacy of a candidate *S. aureus* vaccine. Pfizer's clinical endpoint study evaluating SA4Ag is being conducted in an elective orthopedic surgical subpopulation consisting of adults undergoing an elective, posterior approach, instrumented, multilevel spinal fusion surgical procedure. Pfizer states that they selected this study population for enrollment into study B3451002 based on the following factors:

- 1) this population has an incidence rate of invasive *S. aureus* disease that is on the higher end of the spectrum for orthopedic surgeries (~ 1.4% within 90 days of surgery), because the procedures are, on average, longer in duration and more complex than other elective orthopedic surgeries;
- 2) the incidence rate of invasive *S. aureus* disease is sufficiently high in this population to permit vaccine efficacy evaluation in a clinical trial;
- 3) there is a high volume of this type of surgical procedure being performed; and

Pfizer states that while the rates of invasive *S. aureus* disease across other elective orthopedic surgical populations are significant, they are low (~0.25% to ~0.5% within 90 days of surgery). Therefore, Pfizer states that conducting a randomized, placebo-controlled clinical endpoint efficacy trial that includes other elective orthopedic surgical populations would make the conduct of such a trial operationally impractical.

Pfizer proposes that vaccine safety and efficacy demonstrated in study B3451002 can be generalized to other elective orthopedic surgical populations, because the B3451002 study

population is a stringent elective orthopedic surgical population in which to evaluate vaccine efficacy and it is representative of other elective orthopedic surgical populations. Pfizer considers evaluation of SA4Ag in the selected study B3451002 population to be a stringent assessment of vaccine efficacy, because this population undergoes a more lengthy and complex surgical procedure and consequently has a higher risk of postoperative invasive *S. aureus* disease. Pfizer asserts that study B3451002 is representative of other elective orthopedic surgical populations with regards to the following patient and procedure-related factors associated with developing a postoperative invasive *S. aureus* infection:

- 1) Patient-related risk factors
 - a. colonization status
 - b. age
 - c. health status
 - d. comorbidities

- 2) Procedure-related risk factors
 - a. duration of surgery
 - b. use and types of implanted biocompatible devices
 - c. length of incision
 - d. wound characteristics
 - e. anatomical structures and tissue types
 - f. allogeneic blood transfusion
 - g. perioperative care (e.g., glycemic control, normothermia, oxygenation, antiseptic prophylaxis)

- 3) Immunopathogenicity of *S. aureus* infections across procedures types
 - a. Source of inoculation
 - b. Early pathophysiology of invasive *S. aureus* disease
 - c. *S. aureus* strains associated with infections
 - d. Presence of cellular and humoral immune components at surgical sites

V. PURPOSE OF NOVEMBER 7, 2017 ADVISORY COMMITTEE MEETING

Invasive *Staphylococcus aureus* infections (i.e., bacteremia and deep wound infections) are a serious complication after elective surgeries and result in significant morbidity and mortality. Based on data reported to NHSN for HAIs that occurred in 2011-2014, SSIs accounted for 36.4% of HAIs reported.¹⁷ Overall, *S. aureus* was the most prevalent pathogen isolated from SSIs (20.7%).¹⁷ To address this unmet medical need⁴¹, Pfizer has proposed a clinical development plan to support traditional approval of their investigational SA4Ag vaccine for use in adults undergoing elective orthopedic surgery.

The purpose of this VRBPAC meeting is to seek input regarding the clinical data needed to support an indication for use in adults undergoing elective orthopedic surgery, with a focus on the extent to which safety and efficacy data accrued in a spinal surgery population can be generalized to other elective orthopedic surgical populations.

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