FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Friday, April 26, 2019

8:30 a.m. to 1:02 p.m.

Tommy Douglas Conference Center

1000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh Hotaki, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Lindsey R. Baden, MD

(Chairperson)

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Associate Professor, Harvard Medical School

Boston, Massachusetts

CAPT Timothy H. Burgess, MD, MPH, FACP
Director
Infectious Disease Clinical Research Program
Preventative Medicine & Biostatistics
Uniformed Services University of the
Health Sciences
Bethesda, Maryland

Nina M. Clark, MD
Professor
Stritch School of Medicine
Clinical Division Director, Infectious Diseases
Director, Transplant Infectious Disease Program
Loyola Medical Center
Maywood, Illinois

Dean A. Follmann, PhD

Assistant Director of Biostatistics

Chief Biostatistics Research Branch

National Institute of Allergy and

Infectious Diseases

National Institutes of Health

Bethesda, Maryland

Michael Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical &

Translational Science

University of Pittsburgh School of Medicine

Division of Infectious Diseases

Director, Antimicrobial Stewardship & Infection

Prevention

Co-Director, Transplant Infectious Diseases

Children's Hospital of Pittsburgh

Pittsburgh, Pennsylvania

Barbara M. Gripshover, MD
Associate Professor of Medicine
University Hospitals Cleveland Medical Center
Case Western Reserve University
Division of Infectious Diseases and HIV Medicine
Cleveland, Ohio

Ighovwerha Ofotokun, MD, MSc
Professor of Medicine
Division of Infectious Diseases
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia

George K. Siberry, MD, MPH
Medical Officer
Adult Clinical Branch, Office of HIV/AIDS
S/GAC Senior Technical Advisor for Pediatrics
U.S. Agency for International Development
Arlington, Virginia

Sankar Swaminathan, MD

Professor and Chief

Division of Infectious Diseases

Department of Internal Medicine

University of Utah School of Medicine

Salt Lake City, Utah

Peter Joseph Weina, PhD, MD

Colonel, Medical Corps, US Army

Branch Chief, Research Regulatory Oversight Office

Office of the Under Secretary of Defense (Personnel and Readiness)

Defense Health Headquarters

Falls Church, Virginia

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Nicholas A. Kartsonis, MD

(Industry Representative)

Sr. Vice President

Infectious Diseases & Vaccines, Clinical Research

Merck Research Laboratories

North Wales, Pennsylvania

TEMPORARY MEMBERS (Voting)

Gregory Burger, PharmD, CPPS, FASHP, NREMT

Medication Safety Coordinator

Risk Management Department

Stormont Vail Health

Topeka, Kansas

Michael D. Caldwell, MD, PhD, FACS
Director, Center for Hyperbaric Medicine and
Tissue Repair
Director, Wound Healing Program
Marshfield Clinic
Department of Surgery
Marshfield, Wisconsin

Maureen A. Finnegan, MD
Associate Professor
Department of Orthopaedic Surgery
UT Southwestern Medical Center
Dallas, Texas

Susan L. Krug
(Patient Representative)
Tucson, Arizona

Steven B. Meisel, PharmD, CPPS
System Director of Medication Safety
Fairview Health Services
Minneapolis, Minnesota

Joy McVey Hugick, BA

(Acting Consumer Representative)

Atlanta, Georgia

Deborah Saine, MS, RPh, FASHP

Director, Quality and Program Development

Valley Partners, Valley Health System

Winchester, Virginia

Adjunct Associate Professor

Department of Pharmaceutical Outcomes and Policy

College of Pharmacy

University of Florida

Gainesville, Florida

Stephanie H. Stovall, MD

Director, Pediatric Infectious Diseases

Medical Director, Pediatric Antimicrobial

Stewardship

Medical Director, Infection Prevention/Epidemiology

Golisano Children's Hospital of Southwest Florida

Lee Health System

Fort Myers, Florida

FDA PARTICIPANTS (Non-Voting)

John Farley, MD, MPH

Deputy Director

Office of Antimicrobial Products (OAP)

Office of New Drugs (OND)

CDER, FDA

Sumathi Nambiar, MD, MPH

Director

Division of Anti-Infective Products (DAIP)

OAP, OND, CDER, FDA

Thomas Smith, MD

Clinical Team Leader

DAIP, OAP, OND, CDER, FDA

Caroline J. Jjingo, MD, MPH

Clinical Reviewer

DAIP, OAP, OND, CDER, FDA

Katherine Schumann, MS

Policy Staff

Office of New Drugs Immediate Office

CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: It is now 8:30. We shall get started.

Good morning. I would first like to remind everyone to please silence your cell phones, including myself, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Alison Hunt. If you're present, please stand. Alison is in the back.

I'm Dr. Lindsey Baden. I'm chairperson of the Antimicrobial Drugs Advisory Committee, and I'll be chairing this meeting. I will now call this meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to my far left.

DR. FARLEY: Good morning. John Farley, deputy director, Office of Antimicrobial Products, CDER, FDA.

DR. NAMBIAR: Good morning. Sumathi

Nambiar, director of the Division of Anti-Infective Products, CDER, FDA.

DR. SMITH: Good morning. I'm Tom Smith, the clinical team leader in the Division of Anti-Infective Products, CDER, FDA.

DR. JJINGO: Good morning. I'm Caroline Jjingo, the clinical reviewer in the Division of Anti-Infective Products.

MS. SCHUMANN: Good morning. I'm Katherine Schumann with the OND, Office of New Drugs Immediate Office, policy staff, CDER, FDA.

DR. CALDWELL: Good morning. I'm Michael Caldwell. I'm a wound surgeon from the Marshfield Clinic.

DR. MEISEL: Steve Meisel, director of medication safety, Fairview Health Services in Minneapolis.

DR. SIBERRY: Good morning. George Siberry, pediatric infectious diseases, Bureau of Global Health, USAID.

DR. GRIPSHOVER: Good morning. Barb Gripshover, Case Western Reserve University, adult

infectious disease.

DR. GREEN: Good morning. Michael Green, pediatric infectious diseases at the Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine.

DR. WEINA: I'm Peter Weina. I'm an infectious disease physician with the Office of the Undersecretary of Defense.

DR. HOTAKI: I'm Lauren Hotaki. I'm the designated federal Officer.

DR. BADEN: Lindsey Baden, adult infectious diseases, Brigham and Women's Hospital; Dana-Farber Cancer Institute; Harvard Medical School, Boston.

DR. CLARK: Mary Clark, adult infectious diseases, Loyola University Medical Center.

DR. FOLLMANN: Dean Follmann, biostatistics, National Institute of Allergy and Infectious Diseases.

DR. OFOTOKUN: Igho Ofotokun, adult infectious diseases, Emory University School of Medicine, Atlanta.

CAPT BURGESS: Tim Burgess, adult infectious

diseases, Uniformed Services University School of Medicine, Bethesda.

DR. SWAMINATHAN: Sankar Swaminathan, infectious disease, University of Utah School of Medicine.

MS. KRUG: Susan Krug, patient representative.

DR. MS. HUGICK: Good morning. I'm Joy McVey Hugick from Atlanta, Georgia. I'm the consumer representative on loan from the Gastrointestinal Drugs Advisory Committee.

DR. SAINE: Hi. I'm Deb Saine, pharmacist director for quality and program development, Valley Health System, Winchester, Virginia.

DR. FINNEGAN: Maureen Finnegan, technologically incompetent. I am an orthopedic surgeon at UT Southwestern, with experience in trauma at Parkland.

DR. STOVALL: Stephanie Stovall, pediatric infectious diseases at Golisano Children's Hospital, southwest Florida.

MR. BURGER: Greg Burger, medication safety

coordinator, Stormont Vail Health, Topeka, Kansas.

DR. KARTSONIS: Good morning. I'm Nicholas Kartsonis, infectious diseases and vaccines at Merck Research Labs, and today I'm serving as the industry representative.

DR. BADEN: I'd like to thank all the committee members for making the time and effort to join us for today's meeting and discussion.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic

at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Dr. Hotaki, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Antimicrobial Drug Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employee or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found in 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the service at which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential

financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of the safety and effectiveness of bacitracin for intramuscular injection for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug, which is the only approved indication for bacitracin for intramuscular injection.

The committee will also consider whether there are other uses for bacitracin for intramuscular injection that could be studied. FDA will present background information on the regulatory history of bacitracin for intramuscular injection and information on the current use of bacitracin for intramuscular injection.

This is a particular matters meeting during which specific matters related to bacitracin for intramuscular injection will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the product at issue.

With regard to FDA's invited industry representative, we would like to disclose that Dr. Nicholas Kartsonis is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Kartsonis' role in this meeting is to represent industry in general and not any particular company. Dr. Kartsonis is employed by Merck Research Laboratories and Merck and Co.

We would like to remind members and temporary voting members that if the discussions

involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have had with the firms that manufacturer bacitracin for intramuscular injection. Thank you.

DR. BADEN: Thank you.

We'll now proceed with the FDA's opening remarks from Dr. Smith.

FDA Opening Remarks - Thomas Smith

DR. SMITH: Good morning. On behalf of the Division of Anti-Infective Products, I'd like to welcome you to the meeting today and thank you for your attendance. Today, we'll be discussing the safety and efficacy of bacitracin for injection for the treatment of infants with pneumonia and empyema caused by staphylococci, shown to be susceptible to the drug. We'll also be considering other uses

that could be studied, and we will not be discussing the topical and ophthalmic formulations of bacitracin.

Bacitracin is a complex polypeptide derived from cultures of Bacillus subtilis. The major component of it is bacitracin A. It's active in vitro against a variety of gram-positive and a few gram-negative organisms. The drug is assayed against the standard activities expressed in units with 1 milligram having a potency of not less than 50 units. It's available as a sterile powder in vials containing 50,000 units, and it's currently marketed under several approved abbreviated new drug applications.

Regarding the indications and usage, the label states that the use of bacitracin for injection is limited to the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug. The drug is to be used for intramuscular administration only. It's prepared by dissolving sodium chloride for injection containing 2 percent procaine

hydrochloride, and dose is 900 to 1000 units per kilogram per day in 2 to 3 divided doses for infants based on their weight.

The label contains a boxed warning for nephrotoxicity, which states that bacitracin for injection may cause renal failure due to tubular and glomerular necrosis. There are instructions for prescribers to monitor renal function, maintain proper fluid intake and urinary output, and to discontinue the drug if renal toxicity occurs.

There is also a warning for anaphylaxis and/or allergic contact dermatitis when the drug is used for non-approved. indications, and the adverse reactions section of the label contains mentions about nephrotoxicity, including albuminuria, cylindruria, azotemia, rising blood levels without any increase in dosage, and there are other adverse reactions, including nausea, vomiting, injection site pain, and rash.

The regulatory history, back in 1948, Upjohn had an approved application for bacitracin sterile powder, 10,000 and 50,000 units per vile. In 1950,

Pfizer had an application that became effective for a 50,000 unit per vial sterile powder. In 1962, Congress amended the Federal Food Drug and Cosmetic Act to require that new drugs be proven effective, as well as safe, to obtain FDA approval. FDA was required to conduct retrospective evaluations of the effectiveness of drug products that had been approved as safe between 1938 and 1962.

FDA contracted with the National Academy of Sciences and National Research Council to make the initial evaluation of the effectiveness of products that have been approved only for safety between 1938 and 1962. The NAS-NRC created review panels, and these panels submitted reports to FDA in the late '60s and early '70s. FDA reviewed and reevaluated the panel findings and published its findings in Federal Register notices. The administrative implementation of these reports was called drug efficacy study implementation or DESI.

For bacitracin for injection, the pre-DESI indications that were reviewed by the NAS-NRC panel included intramuscular injection in the treatment

of infections caused by bacitracin's sensitive organisms resistant to penicillin and other antibiotics; local injection into circumscribed areas such as furuncles, carbuncles, or abscesses, in conjunction with intramuscular administration, use by intrathecal, intraventricular, intracisternal, or intracerebral injection in the treatment of various neurosurgical infections; and locally by topical application in the treatment of susceptible infections of skin, eye, nose, throat, surgical infections with soft tissue and bone, and prophylaxis and burns.

FDA published a DESI notice in 1970 for bacitracin drug products and found that bacitracin for injection was probably effective intramuscularly for the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug, and topically in solution for superficial infections caused by susceptible organisms.

The notice stated that applicants had 12 months to obtain and submit data to provide

substantial evidence of effectiveness for a drug that was deemed probably effective. Bacitracin for injection was also found to be possibly effective in conjunction with intramuscular administration for susceptible nonsurgical or neurosurgical infections, and topically for treatment of skin, eye, nose and throat infections, and in compresses or installations for secondarily infected wounds, ulcers, and pyodermas.

The notice for these indications stated that applicants had 6 months to obtain and submit data to provide substantial evidence of effectiveness.

In 1972, FDA published an amended DESI notice for bacitracin sterile powder. This notice was found to be effective intramuscularly for the treatment of infants with pneumonia and empyema by staphylococci. The basis for this determination appears to be a letter from the NAS-NRC panel on anti-infective drugs' chair who stated that they had used the drug in two such instances in the past year, and as might be expected, the drug performed quite well.

No other medication presently available would have fulfilled this role since vancomycin is too toxic for use in small children. The other indications that had previously been found to be probably effective or possibly affective were reclassified as lacking substantial evidence of effectiveness because no new evidence had been submitted.

In 1984, the Anti-Infective Drugs Advisory Committee reassessed the risks and benefits of bacitracin for injection for the treatment of infants with pneumonia and empyema. The committee at that time recommended withdrawal of bacitracin for injection from certification because of an unfavorable risk-benefit assessment. The committee noted a significant risk of nephrotoxicity and the availability of alternative drugs for the treatment of staphylococcal pneumonia in infants. None of the 5 committee members believed that bacitracin for injection was safe and effective for its approved indication.

Following the 1984 advisory committee

meeting, bacitracin for intramuscular injection remained on the market with the current sole approved indication, treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug. We are aware of no evidence regarding the use of bacitracin for this indication over the past several decades. We are, however, aware of substantial use for unapproved indications, primarily in surgical settings, and this is the reason for assessing this drug once again.

The outline for today's session, we'll have an FDA presentation from Dr. Jjingo about the labeled indication and current uses. There will be an industry presentation from Xellia Pharmaceuticals. We'll have time for an open public hearing, and then there will be two questions for the committee.

The first question is whether the benefits of bacitracin for intramuscular injection outweigh the risks for its approved indication of the treatment of infants with pneumonia and empyema

caused by staphylococci shown to be susceptible to the drug. If yes, we ask that you provide any recommendations concerning labeling. If no, please provide your rationale. We also would just appreciate any additional comments or thoughts regarding your vote.

The second question is a discussion question regarding whether there are uses for bacitracin for intramuscular injection other than for the treatment of infants with pneumonia and empyema caused by staphylococci that could be studied. Thank you.

DR. BADEN: Thank you, Dr. Smith.

We will now proceed with the FDA presentations. Dr. Jjingo?

FDA Presentation - Caroline Jjingo

DR. JJINGO: Good morning. My name is Caroline Jjingo, and I am a clinical reviewer with the Division of Anti-Infective Products, and today I will be discussing both the labeled indication and current uses of bacitracin for intramuscular injection.

Specifically, I would like to address the following topics. First, bacitracin for injection for treatment of pneumonia in infants, which is, as Dr. Smith said, the labeled indication, where I will then go on to discuss a summary of the relevant literature pertinent to this indication. I will then go on to discuss current uses of bacitracin for injection, which will include both utilization data obtained from our OSE colleagues, the drug utilization teams, as well as safety analyses conducted by both the division as well as our OSE colleagues in the Division of Pharmacovigilance.

As stated earlier, bacitracin is a mixture of polypeptides which acts by interfering with bacterial cell wall synthesis. Bacitracin is active against gram-positive organisms, including Staphylococcal aureus and streptococcal species. The only labeled indication for bacitracin is limited to the treatment of infants with pneumonia and empyema by staphylococci shown to be susceptible to bacitracin. It's noted that there

are currently no FDA recognized breakpoints for bacitracin.

Labeling includes a boxed warning stating that the drug may cause renal failure due to tubular and glomerular necrosis. There are several FDA anti-bacterial drugs for the treatment of staphylococcal pneumonia in infants, including anti-staphylococcal penicillins, such as oxacillin; first-generation cephalosporins such as cefazolin, vancomycin, linezolid, and clindamycin.

We conducted a literature review looking at the uses of bacitracin in infants with staphylococcal pneumonia. We retrieved a total of 4 articles published between 1957 and 1972. No relevant publications were identified in our search after 1972. All 4 publications, which I will go on to summarize, provided very limited and largely descriptive information on the use of intramuscular bacitracin for the treatment of staphylococcal infection in infants. Bacitracin was administered intrapleurally in neonates with empyema.

I wanted to discuss now the first two

articles, both of which were published in the late 1950s. Just to provide you with a background, this was in a setting where there was increased staphylococcal infections in parallel with a growing penicillin resistance, and staph pneumonia was found in early infancy and can be fatal in that particular demographic.

Koch et al. in 1957 published a retrospective, single-center case series of 480 pediatric patients with various staphylococcal infections in children between the ages of 2 days old to 15 years old. Eighteen percent were reportedly less than 2 months of age. The number of children with staphylococcal pneumonia treated with bacitracin and their clinical outcomes was not described, and bacitracin was used in conjunction with chloramphenicol in this particular study.

Pryles et al. in 1958 published a retrospective case series of 24 patients, all of whom had staph pneumonia. They ranged from the age of newborn to 42 months. Nineteen of the 24 patients had complications of pneumonia with

empyema. All patients were given parenteral antibiotics, and bacitracin in 7 patients who had empyema was instilled intrapleurally at a dosage of 5,000 to 10,000 units and given over 2 to 8 days without adverse outcomes. The authors recommended local administration in severely ill infants with massive empyemas. However, they warn that considerable caution should be exercised while doing so. No nephrotoxicity was observed in the 7 patients.

Gourlay et al. published in 1962 a retrospective single-center case series of 176 patients with staphylococcal pneumonia, 35 of whom also were noted to have empyema. The number of children treated with bacitracin and their clinical outcomes was not described. Bacitracin intramuscular injection was described as a recommended therapy in desperately ill patients. However, with the arrival of newer antibiotics such as kanamycin and vancomycin, these were used preferentially over bacitracin; at least that's what the authors had recommended.

Geley et al., the final publication, published a series of 273 cases from 1954 through 1956 and 1957 through 1970. 152 of these patients had Staph aureus. A singular reference is made to bacitracin used in combination with neomycin, which was described as quote/unquote "excellent local antibiotics for installation into the pleural cavity in neonates and infants with empyema." It was unclear, however, how many children in this case series received this drug combination, as well as the clinical efficacy or microbiologic outcomes in response to this combination therapy.

I will now go on to discuss current uses of bacitracin. Analyses of bacitracin utilization data and review of the literature suggests that bacitracin for injection is currently administered mainly for unapproved uses. Primary usage is in the operating room.

Our drug utilization colleagues conducted, using an IQVIA database as the data source, analyses of bacitracin for intramuscular injection in the hospital setting, the primary setting of

care, based on sales distribution data from manufacturers over a 3-year period, from 2015 through 2017.

Annually, over this 3-year period, an estimated 2.3 million patients were administered bacitracin for injection in the hospital setting. This data stratified by age demonstrated that the majority of usage was among patients ages 17 years of age and older. Pediatric patients aged 16 years or younger accounted for approximately 2 to 3 percent of the total patients annually. Specifically, patients ages younger than 1 year old accounted for less than 0.5 percent of all total patients.

Of note, this data source does not include specialty hospitals such as stand-alone children's hospitals or federal hospitals. However, pediatric units and non-federal hospitals were captured. Therefore, this patient-use data may underestimate total pediatric utilization because of these limitations. However, the overall conclusion from this utilization data demonstrates that bacitracin

for injection is largely being used in adult patients.

This next graph shows the same data stratified by location of care with a particular focus on data from 2017. As we could see in 2017, the majority of bacitracin for injection use was reported to be in the OR setting compared to other units in the hospital. No data was captured for injectable bacitracin use in either the pediatric intensive care unit or the neonatal intensive care unit within this data source.

Please note that the total percentages across locations is greater than 100 percent, as multiple administrations across all locations were captured. Patients who received more than 1 administration of bacitracin were counted more than once.

Given what we've found in the utilization data, we looked at the literature, the existing literature, which was comprised mostly of retrospective, observational, single-center studies reporting off-label uses of bacitracin for

injection. Most commonly identified uses of bacitracin for injection was as a component of intraoperative irrigation solutions.

For example, in the plastic surgery literature, bacitracin in combination with other antibacterial drugs was used during breast reconstruction procedures for the prevention of a capsular contraction, which is a well known complication of this procedure and believed to be related to subclinical infection by some.

In the orthopedics surgery literature, bacitracin is used for irrigation and debridement of prosthetic joint infections. Cardiologists have used bacitracin as an antibiotic irrigation solution for prophylaxis against cardiovascular implantable electronic device infections. However, it appears that these practice patterns of bacitracin usage vary considerably between institutions as well as between individual surgeons.

Given what we've found in the literature, we looked to see what professional societies had to

say and weighing in generally on the topical antimicrobials for the prevention of surgical site infections. So this is not only bacitracin but any topical antimicrobial.

In joint clinical practice guidelines published in 2013, societies such as the Infectious Disease Society of America, and the Society of Healthcare Epidemiology of America, as well as two others, stated that there is no additional benefit of topically administered antimicrobial irrigation solutions, pastes, or washes when used as adjuncts to parenteral antimicrobial prophylaxis, and that additional data are needed to support this practice.

The American College of Surgeons and Surgical Infection Society states that there is insufficient evidence to recommend routine use of topical antimicrobial therapy to decrease the risk of surgical site infections. In 2017, the Centers for Disease Control and Prevention published a guideline for the prevention of surgical site infections, which stated that there are uncertain

trade-offs between the benefits and harms of intraoperative antimicrobial irrigation, and that no recommendation could be made regarding its use.

Now we'll go on to discuss bacitracin related safety concerns, which there were primarily three: nephrotoxicity, much of which was characterized in the early literature from the 1940s to 1950s, and it was characterized by renal, tubular, glomerular necrosis, proteinuria, albuminuria, elevations in BUN, and decreases in renal function. Hypersensitivity has also been quite well characterized, including anaphylaxis.

Bacitracin is cited as the eighth most frequent allergen in North America among topically administered drugs, and this was in a publication from just last year, 2018. Medication errors where bacitracin irrigation solutions were inadvertently administered intravenously have also been reported.

With a focus on nephrotoxicity, in 1950, Miller et al. in a publication detailed the nephrotoxicity of bacitracin in mouse, rat, and monkey studies. In the mouse and rat studies,

tubular degeneration and necrosis was observed, and in monkey studies, proteinuria and glycosuria were observed. A study of healthy volunteers showed occurrences of proteinuria, urinary cast, and reductions in renal function in patients, healthy volunteers who received bacitracin.

Meleney et al. in 1949, in a case series of 270 patients, largely surgical who received 50,000 units of bacitracin every 6 hours, administered locally or systemically, reported also experiences where albumin appearing in urine 2 to 3 days after the initiation of bacitracin treatment was observed. Active urine sediments on urine microscopic analyses, namely urine casts, were observed; elevations in blood nitrogen or uremia; declines in glomerular and tubular filtration; and also specific gravity.

Miller et al., again in their 1950 publication, also noted that 148 patients with early syphilis received parenteral bacitracin. All 148 developed proteinuria and casts during the course of therapy. Hematuria was rare.

We conducted, in terms of safety, a PubMed search for articles related to adverse events associated with use of bacitracin in irrigation solutions or in the context of surgical procedures. A total of 12 relevant citations were retrieved, and they were published between 1979 and 2017.

Ten case reports involving 10 patients were included. Of the 12 case patients, 11 cases reported anaphylactic reactions; 9 following bacitracin irrigation; 1 with a medical device which had been soaked in bacitracin; and 1 patient a bacitracin-soaked gauze applied to the surgical cavity. In many instances, these patients actually had prior exposure to bacitracin, and then upon a second re-exposure, they had an anaphylactic reaction. There was one case of a mediastinal irrigation resulting in an increase in serum bacitracin levels and an increase in serum BUN levels. However, notably, serum creatinine and urine output remained normal.

Our OSE colleagues in the Division of Pharmacovigilance conducted a FAERS search, FAERS

standing for FDA Adverse Events Reporting Systems, and this search was through December 12, 2018 and included any reports of parenteral use of bacitracin through such administration through intramuscular, intravenous, or intraperitoneal administration. They identified a total of 35 cases: 24 cases where bacitracin was used as an irrigation solution and 11 cases in which bacitracin was used intravenously.

Most cases were in patients 17 years of age and older. Most frequently reported MedDRA preferred terms for patients who received bacitracin irrigation in descending order included hypersensitivity, dermatitis, application site reactions, anaphylactic reaction, anaphylactoid reaction, and hypotension. The most frequently reported MedDRA preferred terms for bacitracin used via intravenous routes included accidental overdose, headache, medication error, photophobia, pyrexia, with 2 cases for each reported preferred term.

In summary, there are several take-home

points I would like to highlight for you. The review of the literature identified very limited information on use of bacitracin for injection in infants with staphylococcal pneumonia, and most of this literature was dated back into the '40s through the early '70s. There are several approved antibacterial drugs for the treatment of infants with staphylococcal pneumonia today.

Use of intramuscular bacitracin for injection is not consistent with treatment guidelines or clinical practice for the treatment of staphylococcal pneumonia in infants. The current uses of bacitracin for injection appears to be primarily in adults in the operating room. Hypersensitivity reactions, including anaphylaxis and nephrotoxicity, are the most commonly reported adverse reactions. Findings of nephrotoxicity, including proteinuria, urinary casts, and reduced renal function, have been reported with systemic and topical use of bacitracin.

In closing, DAIP would like to acknowledge and express our appreciation to our Office of

Surveillance and Epidemiology colleagues for their contributions to this presentation, mainly the Division of Epidemiology II, the Drug Utilization Team, Dr. Grace Chai; Dr Rajdeep Gill; Dr. Jennie Wong; and our colleagues in the Division of Pharmacovigilance II, Dr. S. Christopher Jones; Dr. Kelly Cao; and Dr. Ron Wassel. I'd also like to thank the OAP and DAIP leadership for their assistance with this presentation. Thank you all for your attention.

Clarifying Questions

DR. BADEN: Thank you, Dr. Jjingo.

We have about 20 minutes for clarifying questions to the agency. If you have questions, please get Dr. Hotaki or my attention, and we'll add you to the list. If you have a direct follow-on to the question, please turn your card, and angle your card this way so we can try to develop themes. But hopefully it's a direct follow-on, so that we're able to thematically address things but also move quickly through the different questions.

I think Dr. Green has first question.

DR. GREEN: Yes. Thank you. This is a general question to the FDA. Perhaps we could have an understanding why in 1984, when a previous version of this committee made a unanimous recommendation to withdraw the drug based on a lack of data for its indication, it wasn't acted upon. I think we need a historical context.

DR. FARLEY: Sure. This is John Farley. We don't know the answer to your question. We've looked, and we're unable to find any information about the agency's decision-making after the advisory committee in 1984. But quite a bit of time has elapsed since that time, and we wanted to provide a new opportunity for experts to discuss and provide advice to us regarding the benefits and risks of this product.

DR. BADEN: Dr. Meisel?

DR. MEISEL: Steve Meisel. That was actually one of my two questions. One question for Dr. Jjingo. The data on utilization, if you pull up slide number 8 and 9, I had a clarifying

question about the age and location of the use.

We're talking here about ages 0 to 16. The approved indication is in infants. Do you have any data that can sub-stratify the 0 to 16 down to the infant population for which this drug is approved?

DR. JJINGO: Sorry. Did you say [inaudible - off mic].

DR. GREEN: Yes. Can you break that down further to -- I mean, 0 to 16 is a pretty broad range and encompasses all sorts of people other than infants.

DR. JJINGO: We have some of our colleagues from the drug utilization team that can hopefully help with this.

DR. BADEN: When you come to the mic, can you please state your name for the record, and everyone should please use a microphone so that the information is in the record.

DR. WONG: Hi. I'm Jennie Wong. I'm from the FDA OSE team. Thank you for the question. Yes, we actually did have a breakdown of the pediatric age. Because the drug is only indicated

in infants, we separated from 1 through 16 and less than 1. It's actually in the more comprehensive review that we did. I'm not sure if it was appended to the backgrounder.

DR. GREEN: Well, can you tell us what the data are?

DR. WONG: Yes, sure. I'm going to go over the 2017, which is the most recent data that we have. For 1 to 16, there was about 85 percent of the patients, and then for less than 1, about 15 percent.

DR. BADEN: But these data are total use. They're not systemic use like IM or IV.

DR. WONG: Yes, that's correct.

DR. BADEN: I think Dr. Burger had a follow-on. No?

Dr. Follmann?

DR. FOLLMANN: I have a couple questions for the FDA. The first one had to do with slide 3 of Dr. Smith, where he said bacitracin for injection is marketed under several approved abbreviated new drug applications. I wasn't familiar with that

mechanism or I don't understand what it is. So if you could just expand on that.

DR. SCHUMANN: This is Katie Schumann from the Office of New Drugs. Sure. Abbreviated new drug applications, short for ANDA, it's the generic drug pathway.

Does that help clarify?

DR. FOLLMANN: Not yet. So they can market it or sell it as something -- it's labeled a certain way.

DR. SCHUMANN: Sure. So it's a pathway by which applicants can show equivalence of a drug to an innovator through generally bioequivalence studies or comparison.

DR. FOLLMANN: I see.

DR. BADEN: So it's not a new set of studies. It shows comparable to an approved.

DR. SCHUMANN: Right. It's --

DR. FOLLMANN: In laboratory-based experiments, not in humans.

DR. SCHUMANN: It depends on the drug, but it's the generic drug approval pathway provided for

by the statute.

DR. FOLLMANN: Okay.

DR. SCHUMANN: Is that helpful?

DR. FOLLMANN: The other question, bacitracin is labeled for injection, but it seemed like a lot of the use was for irrigation. So it wasn't for injection? I'm a little confused about that, because it sounds like they bill for injection, but they don't use it for injection. They use it for irrigation, which seems to be different than injection.

DR. JJINGO: Yes. From my review of the literature, it seems like they use it in a solution, so not necessarily as an -- and they may just use it in combination with normal saline or other kinds of antimicrobial agents, but it's usually as a solution.

DR. FOLLMANN: But since it's labeled for injection --

DR. BADEN: The distinction you're making is between a wash as opposed to an intravenous or an IM administration.

DR. JJINGO: Yes. And from what I saw, at least in my reading, was most often as a wash.

DR. FOLLMANN: Thank you.

DR. BADEN: Did you have a comment?

DR. WONG: I would like to add that's why we did the --

DR. BADEN: Please state your name. Thank you.

DR. WONG: Oh, sorry. Jennie. That's why we actually did a location of care data because we weren't able to tell the difference between the routes. So the stratification of the location kind of tells us that it was mostly used for the OR setting, so that's kind of letting us know that it may be used for irrigation purposes, but we're not entirely sure.

DR. BADEN: Dr. Finnegan?

DR. FINNEGAN: I actually have several questions. The first is I had to go back to the books. Bacitracin is really bacteriostatic instead of bactericidal, although there was a comment that if it's a high enough dose, it becomes

bactericidal. So do we have any data on whether we know the doses that were given are bactericidal or just bacteriostatic?

(No audible response.)

DR. FINNEGAN: Okay. I cannot out-do infectious disease. I come from Southwestern. They will be really unhappy if the orthopedic surgeon out-does infectious disease.

DR. JJINGO: Really, in the literature that we saw, they didn't go into --

DR. FINNEGAN: Any detail.

DR. JJINGO: -- detail.

DR. FINNEGAN: My second comment, I guess, is that it appears that for the irrigation, it's used in spaces that are very walled off. And I know the literature says that it doesn't cross the blood-brain barrier, so I'm wondering if in fact it doesn't diffuse across enclosed spaces, which would be if you're doing an infected prosthesis, there's usually a really good thick wall around it. So maybe that's why it works fairly well without significant problems.

My math is probably not great, but if you take your FAERS data and you take your utilization data, it looks like the actual incidence of problems was less than 1 percent and actually probably less than 0.1 percent.

Then my last comment or question is if you take your usage of locations, it looks like it's used in patients who are in extremis or who have problems that nothing else is working for, so I wonder if that's a consideration.

DR. JJINGO: With regard to your last point about patients who are an extremist -- and again, I'm not a surgeon, but from my review of the literature, it didn't seem to -- it seems like individual institutions or surgeons who have their own practice, for whatever reason, of using bacitracin, whether it's something that they inherited from their residency training. But it didn't appear from my review of the literature that these patients were an extremis. It seems like it's just adopted practice by different surgeons and different institutions, and that's variable.

It was mostly just for the hopes that it could prevent downstream infections.

DR. FINNEGAN: That's probably fair. The only thing I would say is if you look at the locations, they're all acute intervention location, so that would be a concern.

DR. BADEN: Just to build on Dr. Finnegan's comment, the way this is coming forward, it's not coming forward as a new application, where we have extensive in vitro data, model data, and an RCT. We're retrospectively looking at what was done when Max Finland was in his heyday developing penicillin, and it's very hard to retrospectively appreciate the issue of the microbiology and having an extensive assessment in vitro because there was no incentive to do that for this meeting.

Is that correct?

DR. JJINGO: At least it seems like that, but the quality of the literature in the '40s was also quite different.

DR. BADEN: No, no. It's not a criticism. I'm just amplifying the observation that normally

we would have an in vitro set of data, which would say it works for this staph, works for this staph, and for MRSA. Those types of data have not been generated because of the nature of this meeting, so therefore, we don't have the corollary information that we'd often think about in terms of dose, route, organism, and preclinical data set.

DR. JJINGO: That's correct.

DR. BADEN: To drill on a slightly different line of question but was already raised, much of the 2.3 million use is in the wash category, we're not sure. However, it looks like some of the use was systemic, and at least if I'm interpreting the data presented correctly, 11 of the adverse events, so to speak, were intravenous. It wasn't clear to me if those 11 intravenous were given inadvertently on medication error or if there is an intravenous or IM administration for an efficacy reason.

If so, I'd be very interested in the last 10-20 years, are there any data on very special cases where it was used systemically? And if so, do we have any information on the condition and the

outcome as a salvage use? The 11 intravenous in the adverse event portfolio suggests to me some may have used it for systemic infection, and I don't know if you have any data on those cases or outcome.

DR. SMITH: Yes. We believe those were all cases of inadvertent administration --

DR. BADEN: Okay.

DR. SMITH: -- and not with the intention of using it systemically.

DR. BADEN: So are we aware of any systemic use -- and I mean IM/IV -- for a serious infection in the last 20 years in a desperate clinical situation?

DR. SMITH: We looked, and we're unable to identify any uses for that --

DR. BADEN: From that way.

DR. SMITH: -- purpose.

DR. BADEN: So therefore, to Dr. Follmann's comment, almost all of the use was in the wash framework, if I may use that characterization.

DR. SMITH: We believe that's correct.

DR. BADEN: Dr. Burger?

DR. BURGER: Greg Burger, Stormont Vail Health, Topeka. I have a question about slide 12, the hypersensitivity reactions. The study that was published in Dermatitis in 2018 says that bacitracin was ranked 8th, and I was curious about the top 7 and how many they ranked.

DR. JJINGO: I don't have that information available to me at hand, at the moment.

DR. BADEN: But that's in the topical setting.

DR. JJINGO: It is listed as a topical, but I don't have --

DR. BADEN: Through the dermatologic allergy community.

Dr. Green?

DR. GREEN: This is a novel question. Mike Green. To the agency, do they know of any other examples where a previously approved drug with a single or maybe a couple of indications, for which there is no longer any use of the drug for its approved indications, have been maintained because

it's been used only off label for which there aren't -- at least we haven't seen the data of efficacy?

DR. FARLEY: Let me just make sure I understand your question. So are there drugs remaining on the market for which the labeled -- virtually there is no use going on apparently for the use for which we found the drug to be safe and effective. Is that fair?

DR. GREEN: So other examples like this, where it has one or maybe several indications for which it's approved, for which there is no ongoing use and hasn't been in this case for a while -- and I'll tell you that I've been in practice for 30 some years and never used it as an injectable drug in the treatment of children, and I'm a pediatric infectious disease specialist.

So are there other examples where it's been allowed to be maintained because it has found an off-label niche?

DR. FARLEY: I'm going to defer to my policy colleague.

DR. SCHUMANN: I don't think we can answer that question. We didn't do a comprehensive look at that when we considered this drug. We were just looking at information related to this drug, so I don't think we're prepared to talk about that today. I know that's not helpful.

DR. GREEN: No. I mean, again, it's obvious. Obviously, if there's a precedent for allowing it to stay, it would be worth knowing, and if there's no precedent -- and if you don't know, that's okay for us to know. That's what I was looking for.

DR. SCHUMANN: I think today the FDA is just thinking about the benefits and risks of the drug for its approved indication, and we're not going beyond that to what the next steps might be. We're looking for advice from you to think about this question.

DR. BADEN: And the approved indication is that singular approved indication?

DR. SCHUMANN: Yes.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Just a couple of clarifications. It does appear to me from the presentation that a lot of the adults use was in the wash, antibiotics wash, either in the operating room -- I'm trying to understand, looking at the toxicity, especially the nephrotoxicity that is associated with the use of bacitracin, how much of that do we see experienced when bacitracin is used as a wash in the OR setting?

DR. NAMBIAR: Hi. This is Sumathi. I'm not sure if we have exact numbers, but certainly nephrotoxicity has been reported with use in irrigation solutions, because the product does get absorbed even if it's instant for irrigation purposes. And depending on the dwell time, et cetera, the incidence of nephrotoxicity can vary. But there are reports of nephrotoxicity.

DR. OFOTOKUN: Do you have a sense of whether that is a common theme? I'm just trying to get -- it looks like we don't have a clear sense of whether the wash is beneficial, but I'm trying to figure out if it is.

DR. NAMBIAR: I think it's hard for us to comment on the rate. As you can see, we are working with very limited data here, but to answer the question, can one get nephrotoxicity with administration other than IM or IV, the answer is yes. It's always very difficult to calculate rates based on postmarketing reports.

DR. BADEN: To rephrase that in another way, I think the question in part is it's very difficult to retrospectively assign causality of nephrotoxicity when you're using it as a wash for an acute other indication, a complex patient. However, are there systematic data that show blood levels? And there were some in the background document, but it seemed anecdotal, and that might be a surrogate about systemic absorption in the wash setting.

DR. NAMBIAR: This is Sumathi. Yes, we do have that information.

Tim, do you want to comment? We've certainly identified publications where systemic levels following those routes of administration are

close to what you would get with parenteral administration.

Tim, do you want to comment?

DR. BENSMAN: Tim Bensman, clinical pharmacology, FDA. Yes, there was a paper looking at intraperitoneal lavage solution, about 50,000 units of bacitracin in 200 mLs/NS. Dwell times were 2 and 5 minutes, and then they suctioned it out. Serum levels were approximate 2 IM 50,000-unit doses.

DR. BADEN: Thank you. And that's what I saw in the background document, and at least for me, it raised the question of could this be something else complicating the care of our patients that we never thought about, given the nature of its use. But there aren't enough systemic data to guide the thinking, but at least there is a surrogate that might imply systemic toxicity.

We have a few more questions. Dr. Follmann?

DR. FOLLMANN: This is just a follow-on to Dr. Ofotokun. In the sponsor's material, there was

a randomized trial where they randomized, I guess, fractures to C. Bactrim [sic] or castile soap, and there was more infection with the bacitracin arm that wasn't significant and more wound-healing problems in the bacitracin arm, which was significant, p 0.3. This is a random trial, and in fractures, they randomized to bacitracin or castile soap, and it didn't show a benefit of bacitracin.

DR. BADEN: Dr. Caldwell?

DR. CALDWELL: I just wanted to inform the discussion a little bit. Surgeons don't wash with these types of solutions, they irrigate, and there's a difference. The amount of force that you use, the amount of solution that you use, the timing, the aggressiveness of it are all important as a piece of the process of irrigating wounds.

We irrigate wounds to get rid of not only bacteria but to also get rid of debris that are present within the area of the wound, both of which are clearly related to ultimate development of infection and wound healing. So I'd appreciate it if we would refer to it as irrigation, not wash.

We don't do laundry.

(Laughter.)

DR. BADEN: Thank you for that clarification. We in infectious diseases do do laundry and windows.

We need I guess two quick follow-ons, then we need to move on to the applicant presentation, or industry presentation.

DR. SAINE: Hi. Deb Saine. My question is related to we're in an unprecedented era of drug shortages, and I wondered if the agency is aware of an occurrence in which all the drugs listed on the bottom of slide 3 have been in a shortage situation concurrently.

DR. NAMBIAR: We'll have to look up our drug shortage information and see if there was a point in time when every one of the listed products were in shortage, but typically we do provide to the public information about drug shortages. I don't know if I can answer the question. There was a point in time when every one of these was not available. I think that would be a little hard to

answer unless we go back and look at the data over a period of time and see if there could have been a day or two when such an incident happened.

DR. BADEN: And that's in conjunction with antibiotic resistance in the organism, because you can have drug shortage or you can have antibiotic-resistant organism and then shortage of the relevant drugs, in that space.

Thank you. We will move to the industry presentation. If there are more clarifying questions for the agency, we will come back to that later in the morning.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting

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We will now proceed with Xellia Pharmaceuticals' presentations, Dr. Anic-Milic. Thank you.

Industry Presentation - Tatjana Anic-Milic

DR. ANIC-MILIC: Thank you. I'm Tatjana Anic-Milic, medical doctor by background. I am a representative from Xellia Pharmaceuticals. I'm heading the medical affairs department. Xellia Pharmaceuticals has a very big interest in the efficacy and safety of bacitracin because we're the producer of API as well as final dosing form. We really appreciate that we are invited to this

meeting to participate in discussion about bacitracin efficacy and safety.

The content of this presentation focuses on the four main topics. The first part of the presentation will be dedicated to a snapshot of published clinical data regarding the bacitracin efficacy, then a slight overview of the efficacy and approved uh, indication. Then we'll switch to the selected alternate uses that we picked from the literature, mainly focused on surgical site infection, as the previous speakers announced already; then local administration for the treatment of surgical site infections and other serious infections; as well as information about oral administration of otherwise intramuscular intended bacitracin.

The last part of presentation will be a safety overview of literature data and FAERS data that we have gathered within the Freedom of Information, and data from Xellia safety database that are provided from our pharmacovigilance service provider.

Just slightly to hover over information that previous speakers have already done, bacitracin is a polypeptide antibiotic produced by Bacillus licheniformis or subtilis tracing. It is active against Staphylococcus aureus, including MRSA, and most gram-positive bacteria, but it is also active against some gram-negative bacteria like meningococci, gonococci, as well as Treponema pallidum and some protozoa.

As was already discussed, exact susceptibility breakpoints are not established for this [indiscernible] drug, I will say, and there was no data on EUCAST breakpoints as well as on the stake [ph] database. So we have limited data on the current susceptibility pattern.

The mechanism of action, bacitracin acts on the peptidoglycan synthesis inhibition, thus destabilizing and disrupting the bacterial membrane wall, and depending on bacitracin concentration and microorganism susceptibility, it could exert either bactericidal or bacteriostatic efficacy. However, amongst systemic diseases, despite this different

microbiological collectivity, only staphylococcal infections qualify for consideration of bacitracin intramuscular therapy according to current prescribing information.

We all know that pneumonia and empyema in infants caused by staphylococci shown to be susceptible to the drug is the only approved indication for bacitracin for intramuscular use, and daily dose in infants less than 2 and a half kilos, 900 units per kilogram, or those which are a higher body mass weight of 250 grams, 800 units per kilogram. This dose can be split into 2 to 3 doses per day. The route of administration is exclusively intramuscular.

Amongst safety, the biggest concern is nephrotoxicity, and because of that, it should not be given with other nephrotoxic drugs, and also appropriate follow up in adequate laboratories should be assured for patients who are scheduled for bacitracin. Also, hypersensitivity for drug, which is most often a consequence of widespread use of topical administration, any sign of

hypersensitivity is contraindicated for intramuscular administration of bacitracin.

This is the snapshot of published clinical data. We are, are under-holders, so we don't have our own clinical studies. We more or less approach the same sources of information like previous speakers, however, maybe our way of presentation is somewhat different. We tried to systematize the different administration, which has been described in the literature and displayed the studies that we have found in PubMed using just the word "bacitracin" and we got more than 4,000 references that we can peg to the dose, which could be the most relevant for today's presentation.

We split this route of administration into three big groups, which is intramuscular administration, local, which excludes topical -- means on the skin -- and oral administration. A result is pretty much clear, which is seen from the timeline from the '40s when bacitracin has been approved until nowadays.

Regarding the different shapes and colors on

this display, the small gray circles represent the studies in which titles or further details have been revealed. For the light blue circles, which varies in size, for the smallest circles, these are representative of studies which are just case reports or studies of case series up to 10 patients. Following by the size, there is noncomparative studies comprising 10 to 50, 50 to 100, or more than 100 patients.

Dark blue circles represent the comparative studies or randomized trials, and it is clearly seen that for surgical site infections, there is the concentration of smaller, randomized and comparative trials, and the study which continuously [indiscernible] since inception of bacitracin to the novel days.

Just to finish with the explanation of the scheme, the pink circles represent the randomized double-blind trials, which are scarce, therefore as already mentioned by other speakers, the quality of evidence of bacitracin use is rather low, and it is probably the reason why in the majority of the

guidelines, there is no strong recommendation for its use in surgical site infection.

To come back to intramuscular administration, it is clearly seen from the available evidence in clinical trials that this route of administration has been employed in early years of bacitracin inception. Ranging from various infections, mainly skin and soft tissue infection, then endocarditis, and scarce evidence on use of bacitracin in pneumonia and lung abscess, and is in sepsis, and there is some sporadic evidence of pericarditis and Waterhouse-Friderichsen syndrome.

To switch to local, excluding topical administration, surgical site infection prophylaxis dominated among the trials, however, there was also some local administration for virus infections, mainly skin and soft tissue infections, as well as in CNS infection, peritonitis, empyema, and mediastinitis, as well as some sporadic evidence in bone infections and even in some protozoa diseases in early days of bacitracin availability on the

market.

There is also some evidence which is approaching the current times, which is surgical site infection, so not just prevention in all surgical site infections, where several studies of smaller sizes have been also performed. Regarding oral administration, there are also several, well-controlled clinical trials in C. difficile diarrhea, which are compared mostly with vancomycin.

There were also some trials and bacterial enteritis, and the prominent use was in '80s and '90s for a surgical site prophylaxis by the oral route in terms of colorectal surgery in regard to the colonization, and also with regard to the contamination in neutropenic patients because of prevention of sepsis originating from the gut.

There were also some studies tackling with vancomycin resistant enterococcus species [indiscernible], the colonization, and there was also some withdrawal in chemotherapy induced diarrhea. So a plethora of clinical trials, but

those which are related to currently approved indication were done in early '60s.

This part of the presentation will be dedicated to efficacy in staphylococcal pneumonia and empyema in infants. The evidence on effectiveness and empyema in infants mostly rely on published data describing bacitracin treatment success from authors' clinical practice.

Koch and Donnell in the late '50s described treatment options they used in the treatment of staphylococcal infections in infants, stating that bacitracin is used in combination with chloramphenicol in the most serious infections, in 23 patients where only 2 children died of empyema and pneumonia, probably at least in one child due to a late diagnosis than on treatment failure. Authors concluded that bacitracin belongs to the treatment of choice in Staph aureus infections, particularly when a high rate of penicillin resistance was noted. The majority of patients' isolated strains, 92 percent were resistant to penicillin and 75 percent were resistant to

tetracycline.

Chloramphenicol and bacitracin in combination with novobiocin and erythromycin at that time have been announced as a drug of choice for the treatment of the most serious staphylococci pneumonia and empyema.

The other evidence is similar in nature. Gourlay and authors reported 176 infants, which are treated with other antibiotics either with bacitracin. There are no exact numbers for how many patients have been treated with bacitracin, but in general, the authors claim that for patients who are desperately ill, they will use bacitracin. The similar conclusion has been made by Diamond, who treated 75 infants and children with staph pneumonia, and the following drugs have been effective in septicemia due to Staph aureus and unresponsive severe infection, mentioning vancomycin, kanamycin, ristocetin [ph], and bacitracin.

Jawetz in a review also claimed that some pediatricians used intramuscular injection of

bacitracin in doses of hundred units per kilogram per day for the treatment of staph pneumonia in infants. More or less, these are the complete evidence on usage of intramuscular injection of bacitracin and Staph aureus infection, pneumonia and empyema.

Corroborating clinical data in adults complement for this condition in infants. There is a case report of a 62-year-old man who has been treated successfully with bacitracin, supported by lung penetration of bacitracin in lungs, based on successful treatment of lobar pneumonia in adults in the second study, where 14 patients have been treated with bacitracin, and cure rate raises to 86 percent. The key pathogens identified were streptococcus pneumoniae and hemolytic streptococcus or both. This study doesn't show any specific MIC values, but implies that sensitivity of these pathogens have been confirmed.

Stating a further iteration of empyema treatment in children refers to three studies in which intrapleural administration of bacitracin has

been performed. Despite interim use score administration, authors supplied bacitracin by installation in pleural cavity. There were more than 150 patients, which are treated in three studies, and the dosage regimes varied from 5,000 to 25,000 units.

Treatment duration was up to 10 days. In all three studies, the success has been described, although in the first study, there was no mention [indiscernible] numbers, but likely the positive outcome was achieved because the authors mentioned a good response, and due to these results, they routinely used bacitracin.

In a study of Geley, there the mortality rate decreased from 11.8 in historical control to 5.7 after treatment with bacitracin, which is almost a double decrease in mortality, which is a very important endpoint. Willital and co-authors reported a decrease in septicemia rate, which is almost 3 times lower than a historical controls, reducing from 65 percent to 21; and also a decrease in abscess formation and re-surgery need, as well

as consequent fibrosis, which is also reduced from 77 to 21.

This fear of nephrotoxicity and from other site reports successful treatment with bacitracin after local administration points for a wide use of bacitracin as a local administration, especially important in intraventricular, intracerebral, intrathecal, intrapleural, intraperitoneal, and for wound irrigation, which is the most prominent topic for today.

It should be considered that in some study -- I cannot point it on the top of my head, anyway, but the studies performed in a PK of bacitracin claimed that after intramuscular administration, the distribution of bacitracin is rapid within the whole body. And after peritoneal and intra-mediastinal administration, there is also reported blood levels of bacitracin. However, after intra-articular, or intraventricular, or administration related to central nervous system, the levels of bacitracin in blood are negligible. Thus, escaping systemic toxicity and having

satisfactory efficacy could be attractive options for local treatment.

Let's move to the surgical site prophylaxis and intraoperative use of antibiotic. Why? Because surgical site infections present a significant burden on the healthcare system with a report of 500,000 cases annually in the U.S., which are associated with the cost of $10 billion, mostly related to the prolonged stay in the hospital and additional procedures as a consequence of non-eradicated infection.

One of the prophylactic measures, which is proposed, is surgical wound irrigation with antibiotics. However, the opinions are divided on this intervention because of lack of high-quality evidence, as has been presented in my previous slide. The major guidelines, ASHP, WHO, CDC, an International Orthopedic Consensus do not recommend routine use of bacitracin in wound irrigation because of insufficient evidence.

However, some results of real clinical practice speaks in contrary of these

recommendations. There are three surveys that we succeed to capture from the literature. The first one was performed in 984 orthopedic surgeons, and the second one in 186 orthopedic surgeons, and the third one was in operating room nurses. In all surveys, it was recognized that at least 16 to 20 percent of users in clinical settings used bacitracin or similar antibiotic for wound irrigation despite lack of recommendation and major guidelines.

Deeply diving into the structure of specialties for mostly used bacitracin as wound irrigation solution, there are orthopedics, general surgery for colorectal and cardiac surgery, and also very prominent use in neurosurgery and spine surgery. When looking on the right-hand side among the antibiotics most often used, there is bacitracin and vancomycin followed by gentamicin and clindamycin. So the data from the real-world speaks to the contrary on the major recommendation from the guidelines.

What are the most often used ways of

administration in wound irrigation or direct application of bacitracin to the wounds, in early days up to the '80s, there was research interest reflecting in published studies on wound spraying. Most often it used bacitracin in combination with neomycin or neomycin and polymyxin in a spray called the Polybactrin. In more recent days, wound irrigation has been more often used either as bacitracin monotherapy or in combination, again, with neomycin or polymyxin.

Furthermore, dose administration can be found in the literature, the administration of bacitracin in bone cement, intracavital instillation, and bacitracin-soaked bioabsorbable sponge placed in the sinus cavity, or just a simple spreading of bacitracin powder over the wound.

To briefly hover the current evidence, there are 7 studies in which bacitracin has been administered as a spray, mostly in combination with neomycin and polymyxin B. In five of 7 studies, the outcome has been judged as positive. In comparison with control group, infection rate has

been reduced 7 times, while in the last 2 studies, there has been negative outcome, which can be associated with the method of operational technique and administration of bacitracin, because in all positive studies, all layers of the wound has been sprayed before and after procedure, while in the last 2 studies, the spray was just before closing the cutaneous layer of the wound. Probably this suggests that in the therapeutic mode, adequate exposure to bacitracin should be achieved in order to bear clinical success.

The second way of administration to the wound is bacitracin irrigation solution. There are also 7 studies of bacitracin use, either as monotherapy as the first two studies performed by Teng and Savitz, where bacitracin has been used in neurosurgery, and the infection rate was zero in comparison. Unfortunately, there was no control here.

The third trial, which is also positive, combined bacitracin and neomycin, and in a fourth trial, bacitracin irrigation has been compared with

powder and compared with irrigation alone. This combination beared much better results than just irrigation.

The fourth study has compared bacitracin versus IV cephalosporin versus combination of the two and no prophylaxis, and bacitracin resulted in zero infection rate while combination of IV cephalosporin resulted in 3 percent of infections, while just Cephalosporin or no prevention resulted in 9 percent of infections of the wound. Also, in spinal infections, it was very well resolved; there were no infections.

Michels in 2003 reported bacitracin and neomycin versus normal saline and found no difference. In this study, bacitracin tracing has been flushed before the wound closure, while in other studies, the continuous irrigation of the wound has been performed, which also could suggest that maybe adequate duration of exposure to bacitracin is needed in order to bear clinical success.

There are also some additional studies in

the same settings in different surgeries, different size of patient groups, and different combination. However, in the majority of studies, the positive result has been obtained after administration of bacitracin, mostly in combination treatment.

There was one negative study in which bacitracin has been compared with castile soap, where in this group, there was 18 percent infection rate compared with 13 percent in control. This study has one distinction from all other studies, that the concentration of solution was very low, being 33.3 units, while in all other studies, 50 or more than 50 units per milliliter has been administered.

DR. BADEN: You have 10 minutes.

DR. ANIC-MILIC: I'm sorry?

DR. BADEN: Ten minutes.

DR. ANIC-MILIC: Okay.

DR. BADEN: Thank you.

DR. ANIC-MILIC: So the optimal strength and volume of bacitracin solution as presented is obviously a problem, and strength and volume varied

occurred across the studies. It ranges from 50 to 2000. Also, other variables have to be taken into account in terms of duration of irrigation, local susceptibility, or also a need for gram-negative coverage.

For the treatment for surgical site infection, there is also some sporadic evidence, which has been positive and several ways of administration. For example, in generator pocket, who was infected and treated with irrigation of baci/poly B and successful in all 4 patients in which it has been performed; also, positive evidence of single-stage revision after periprosthetic total knee infection, where eradication rate was 69 percent. Also, in some cases, successful treatment with bacitracin has been obtained in vascular graft infection in the groin, and also after median sternotomy infection.

An interesting point also is local bacitracin administration and treatment of CNS infections, where bacitracin has been administered in a whole range of brain infection and IDS

[indiscernible] structures. Infection cure rate varied from 71 to 100 percent, and the drug has been administered by intrathecal epidural, intracerebral, intraventricular or subdural, intracranial, and topical dressing administration.

Regarding the toxicity at local site of infection, just for an illustration case, patients with multiple brain abscesses and spongioblastoma received in total 250,000 units intracerebrally without any apparent CNS symptoms.

I will just briefly hover through this oral administration. Although bacitracin is approved and provided as a vial for intramuscular administration, it has been also used as a powder and a solution for treatment of C. diff associated diarrhea compared to vancomycin, which is in fact also used as a [indiscernible] powder and dissolved for oral administration and approved for this. It is interesting that regarding clinical response and relapse rate, they were comparable, however, vancomycin outperforms in microbiological success.

The second study was pretty much in the same

direction, as well as outcomes of meta-analysis. In general, it could be seen that despite certain efficacy to C. diff, this is inferior to other treatments, we don't think that C. diff is something where bacitracin could find its place. Maybe one potential additional use is vancomycin resistant Enterococcus faecium decolonization.

There are 4 studies in which administration of 25 to 500,000 units for 10 days led to decolonization, after the majority of other treatments were unsuccessful. However, Weinstein's study suggests that after initial success and after follow-up, which was up to 100 days after the end of the treatment, microbiological rate and the control in baci group were pretty much the same, so it was just a transient effect.

There was one case report in which a 25-year-old patient with leukemia developed VREF bacteremia, and after all treatments with tigecycline, rifampin, quinupristin-dalfopristin, linezolid, and ampicillin, which was successful, the administration of bacitracin solved and cleaned

the gut within 48 hours.

Switching to bacitracin safety, bacitracin is over 70 years in the clinical field. Intramuscular use was ceased in the '60s due to nephrotoxicity. In '78, Eichenwald reported that adverse renal effects were rarely found when bacitracin was used in early infancy, even claiming that it is better tolerated than vancomycin in this early age.

Local administration, especially surgical wound irrigation for surgical site infection prophylaxis and treatment, gained, again, acceptance based on research interest that is obvious from published data. Widespread use of topical bacitracin product for the treatment and prevention of superficial infections caused a hypersensitivity problem. I have a date, that dated in 1992, bacitracin was 7th, although Julie [ph] pointed that in later ages it became 8th. This is probably because of widespread use of topical bacitracin. And just a brief hover over DailyMed, it can be identified in more than 500

bacitracin-containing products.

The key safety problem is nephrotoxicity. I will not repeat a lot of previous presenters' claims, which are pretty much the same. Pain at the injection site is solved by additional procaine, 2 percent to the saline, as a [indiscernible] on top of the intramuscular injection formulation, and also less typical is loss of appetite, nausea, and vomiting.

Regarding anaphylaxis, we also made a PubMed search and identified pretty much the same number of anaphylaxis across different studies, which investigated bacitracin in wound irrigation, laminectomy, nephrectomy, et cetera. Anaphylaxis has also been reported after tissue irrigation or implantation of bacitracin-soaked implants, and all reactions occurred in the operating room, which could be let's say the silver lining because all intervention procedures and educated personnel is present, and all anaphylaxis resolved without sequelae.

The history of skin reaction has been often

identified in patients with anaphylaxis, which suggest that a careful history should be taken from the patient if there is a plan for administering some kind of wound irrigation because anaphylaxis may occur in higher incidence.

By searching FAERS data, we have identified, since inception of FAERS in 1969 through the end of 2018, 637 reports related to bacitracin. Out of them, 216 events were classified as serious. From these reports, we just picked up reports based on literature data, which are most prominent after intramuscular or local administration and are most important. We have identified 37 reports of anaphylaxis and 9 reports of renal or urinary disorders.

Our data from our pharmacovigilance safety provider identified, just from the literature, 2 individual case safety reports, both related to bacitracin ointment administration. Our pharmacovigilance system just confirmed that, based on the evaluation of safety data and benefit-risk analysis, the current risk-benefit ratio of

bacitracin remains unchanged.

In conclusion, the risk-benefit ratio for bacitracin, based on published data and data on safety, seems that it is not jeopardized because there is no direct evidence that any of the newer agents outperforms bacitracin efficacy in infants with staph pneumonia and empyema. This should be also considered in the era of multidrug resistance and pandrug resistant pathogens, where bacitracin may still be the life-saving treatment option in individual patients, of course in line with limitations and prescribing information.

Regarding alternate use, the most prominent is wound irrigation, which obviously is the option which is widely used but needs optimization and standardization in order to provide the best care for the patients. In that context, anaphylaxis may occur. It is a serious adverse event, however, based on available data, it seems that it's still pretty rare and reversible.

With that, I would like to thank you for your attention. I apologize if I missed the

timelines, and thank you for your attention.

DR. BADEN: Thank you very much for covering so much ground in such a short amount of time.

As it is 10:10, what we'll do is we will go to the break and resume at -- can we start a little bit early or should we start at 10:30?

Do we need to start at 10:30? The break is supposed to be 10:15 to 10:30, so I want to keep the open public hearing session where it's supposed to be given the requirements around that.

Can we start at 10:25? Yes. So we will take a break, start at 10:25. We'll start with the open public hearing session, and then afterwards move to clarifying questions, and then through the rest of the meeting agenda. Thank you.

Members of the committee, please remember not to discuss issues before the committee during the break, and we'll resume at 10:25.

(Whereupon, at 10:12 a.m., a recess was taken.)

Clarifying Questions

DR. BADEN: We will now resume, and we will

now resume with the open public hearing portion of the meeting.

Both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public --

It will have to be done before OPH. Then, can OPH be substantially delayed? Up until 11, because the clarifying questions will take more than a few minutes.

I apologize. We will go back to the clarifying questions for the industry colleagues. For those on the committee who have clarifying questions, given the pre-break presentation, please get my or Lauren's attention, and we will start the process as we usually do.

Dr. Finnegan?

DR. FINNEGAN: Was your MRSA data solely on the oral GI environment or was it in other environments?

DR. BADEN: If you can come up to the microphone and then tag team the questions, that

will be appreciated.

DR. ANIC-MILIC: Oral administration of bacitracin has been studied for C. diff infections and for vancomycin resistance and enterococcus faecalis.

DR. FINNEGAN: Correct, but did you study it or did it work in any other MRSA infections that were non-GI?

DR. ANIC-MILIC: It has been tested for muscular wound infections, so with administration and wound irrigation of different sources like intra-abdominal infections and also in neurosurgeries. But it is used in one study. I don't have this -- the last study [inaudible - off mic] was very impressive, which is surprising based on our previous data on Staph aureus.

It was on slide number 20, one single stage of revision of acute peri-prosthetic total knee infection has been studied, and irrigation has been performed with combination of Betadine and Dakin solution and bacitracin. On the right-hand side table, you can see that a staphylococcus and known

MRSA has been identified in 4 to 5 [indiscernible] patients, and success was 58 percent success rate. MRSA has been identified in 5 patients, and the success rate with this combination, it was not monotherapy; it was 20 percent only.

Surprisingly, better results have been obtained with pseudomonas, probably not owing to bacitracin activity, and maybe other interventions like Dakin solutions, which is hypochlorite and kills everything, and maybe better than, which is antiseptic.

DR. BADEN: Follow-on, or if you have a follow-on, please do the card thing so I can track things. Dr. Green?

DR. ANIC-MILIC: Of course, in early evidence, it was effective, but we don't know the exact rate in empyema and Staph pneumoniae, studies for which we don't have such precise data.

DR. GREEN: But just to clarify, at least according to your slide -- this is Michael Green -- these were done in combination with IV

therapy, right? So this is not monotherapy given alone.

DR. ANIC-MILIC: Which indication?

DR. GREEN: The ones that she was asking for. When you were referring to --

DR. ANIC-MILIC: Slide 20?

DR. GREEN: -- slide 20, it looks like for both the top bullet and the bottom bullet, it specifies with systemic therapy and combination.

DR. ANIC-MILIC: It was intraoperatively, and after IV, post-operative treatment with antibiotics has been followed.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Studies of bacitracin in community-acquired MRSA have shown that the majority of strains are resistant to bacitracin. There's even a suggestion that by eliminating competing bacteria, bacitracin increases the colonization with MRSA.

DR. ANIC-MILIC: You are referring to recent data or the data in early days, '50s, '60s?

DR. SWAMINATHAN: I'm referring data in

emerging infectious diseases. I can't give you the exact date, but it was within the last year or so.

DR. ANIC-MILIC: Okay. Thank you.

DR. BADEN: Just one general comment to all of us. The focus of this meeting is on the approved indication and how to evaluate that 50 years later. There are many, many other uses that are of great interest to all of us, but that's not charged to us. So as we think about our questions and how to deepen our understanding, that line of investigation is very important.

Dr. Clark, A follow-on question or no?

I'll come back to you. Dr. Clark?

DR. CLARK: My question was regarding more to the discussion point that's coming, but a question in my mind, as Dr. Green kind of alluded to, is how much additional benefit the irrigation gives to systemic antibiotics.

On slides 15 to 17, where you list all the studies where bacitracin was used as prophylaxis, can you say that how many of these systemic prophylaxis was given as well?

DR. ANIC-MILIC: That is hard to answer precisely on your question. Slides 15 to 17. In the majority of studies, bacitracin has been administered during the operation, and it is not stated or not investigated in our analysis whether this intervention has been add on intravenous, except in a study of Kartush, when bacitracin was compared with IV cephalosporin. In fact, a combination of bacitracin and IV cephalosporin, where bacitracin irrigation beared better results than combination or IV administration only.

So it could be concluded indirectly that combination, when baci has been add-on on IV cephalosporin or less effective than bacitracin locally alone, which I agree can be further studied.

DR. BADEN: Dr. Meisel?

DR. MEISEL: Steve Meisel, a follow-up question to that. Most of those studies, as I look at them, occurred in a time frame prior to the understanding of modern surgical site infection prevention tactics, the skin cleaning, the OR

temperatures, the antibiotic timing, and a thousand other things that we do.

Do you have any data to show that using modern surgical site infection prevention tactics, that irrigation with bacitracin offers additive value?

DR. ANIC-MILIC: I could just point out the recent study made by Lawrence, where the authors based investigation on 300 patients. This is presented on page 17, slide 17, for a pancreaticduodenectomy. They compared bacitracin, which was part of a perioperative bundle, which is also including the placement of periwound ring, then bacitracin solution, and use of gloves, which are changed during the operation.

This bundle, bundle which contains bacitracin in comparison with no perioperative bundle, beared success. So the infection rate was 11 percent in comparison with control, which was 22 percent.

DR. MEISEL: But that bundle, the control group there didn't use all of the other tactics

that we have grown accustomed to, correct? It was bacitracin plus all that stuff --

DR. ANIC-MILIC: Yes.

DR. MEISEL: -- versus basically nothing.

DR. ANIC-MILIC: Not one of this stuff.

DR. MEISEL: Yes. Thank you.

DR. ANIC-MILIC: It is not too easy to distinguish the contribution of each of element, however, the whole bundle reduced the infection rate by half, so 11 versus 22.

DR. BADEN: Dr. Swaminathan, a follow-on?

So a different line of question. The issue of systemic use intravenous/intramuscular, in the 5 years that you all have been marketing this product, are you aware of systemic use by intramuscular IV use for serious invasive infection?

DR. ANIC-MILIC: Unfortunately, we don't have the tools to distinguish use of our drugs for intramuscular use versus other uses because we are just monitoring the sales --

DR. BADEN: Sure.

DR. ANIC-MILIC: -- of bacitracin for intramuscular. We just can monitor the feedback from reported adverse events, and so far we didn't receive any of them, so we are on the market in September 2014, and we just collected data from the published literature, and there was two reports related to topical administration. So no one has reported anything regarding to our drug.

DR. BADEN: No. Thank you. I just wanted to make sure if there were data available, the use for invasive infection.

DR. ANIC-MILIC: We would like to be able to distinguish, but, however, we don't have tools we can just follow IMS data and monitor the sales of our drugs. For this IQVIA, data is probably not publicly available.

DR. BADEN: Thank you.

Dr. Burgess, do you have a question?

(No audible response.)

DR. BADEN: Dr. Caldwell?

DR. CALDWELL: In the studies where bacitracin was compared to a vanco for oral use in

C. diff, treating C. diff, is there any follow-up as to the stool presence of VRE following that treatment because of the high incidence of VRE that occurs with oral vancomycin use, particularly frequently for C. diff?

DR. ANIC-MILIC: That is interesting because when comparing vancomycin and bacitracin in the treatment of C. diff associated diarrhea, the clinical response was similar, and the relapse rate was similar as vancomycin. However, when monitoring -- so if we talk about the follow-up, we can measure it by relapsed rate, which was I think 33 versus 20 percent baci versus vanco, which was statistically insignificant.

However, when looking at the microbiological response, vancomycin is definitely superior to bacitracin. However, there are some work that suggests the pharmacodynamic effect of bacitracin on C. diff toxins, and maybe this is the reason why clinically they are pretty much equal or a non-significant difference exists between vanco and bacitracin, because the disease is caused by toxin

and not by C. diff itself. But if you look at the eradication of C. diff, then vanco is better because --

DR. CALDWELL: I think I may have been misunderstood. What I was asking was not about residual C. diff, but what happens to the E. faecium or E. faecalis that's present within the gut --

DR. BADEN: The flora.

DR. CALDWELL: -- right. After that exposure to vancomycin, does it change? If you're using bacitracin versus vancomycin, what happens to your incidence of VRE, vancomycin resistant enterococcus in the stool?

DR. ANIC-MILIC: If I understand well, bacitracin has been effective against vancomycin-resistant enterococci. However, this treatment has been followed for 24 weeks, then it was successful despite all other treatments. But after 100 days of follow-up, the non-responder and treatment group rate was pretty dissimilar, which means that bacterial flora returns to previous

state. That was not a long-term effect of bacitracin, based on the last study that has been displayed in this presentation.

DR. BADEN: Dr. Finnegan, do you have a follow-on?

DR. ANIC-MILIC: So a follow-on was --

DR. BADEN: Dr. Finnegan, do you have a follow-on question?

DR. FINNEGAN: It is a follow-on on the vancomycin/bacitracin events. Even though her CDC statement on slide 12 says that the CDC recommends no antibiotic powder in wounds that in fact is not exactly being followed, there are two studies in 2018, one in JBGS and one in Neurosurgery, where there is a significant reduction in deep infections with putting vancomycin in the wounds. So we know that vancomycin will eventually come up with VRE, so there may be a place for that.

The other comment I'd like to make is that even though intravenous antibiotics are wonderful, when you have a surgical infection, quite often that they don't get to the site, and that's one of

the reasons for using something in your irrigation or in the walled-off area as well.

DR. BADEN: Ms. Hugick?

MS. McVEY HUGICK: Joy McVey Hugick. Because FDA's data was limited and didn't include specialty hospitals such as children's hospitals, I was curious in your monitoring of sales data, if you saw what it looked like as far as children's hospitals, and/or if you know if anyone's using it for its indication. I'm guessing no, but I'd love to hear your insights.

DR. ANIC-MILIC: Yes. I'm not assigned to talk about sales data, however, I just can say that the sustained use of bacitracin, based on our sales data, is presented nowadays or maybe when slightly increased. This also indicates that it is used in clinical settings, and based on FDA data, it is obviously not in children.

DR. BADEN: A follow-on, but it's to the agency. My understanding from the background material is Xellia is about 20 percent of the sales of bacitracin. As we are trying to understand how

it's actually used, there are those institutions not included, but this industry group is a fraction of the overall sales, if we can use that as a use marker, but that Xellia is a minority of the overall use that we're aware of, if I remember the background data properly. I think that's one of the themes I hear, is trying to understand the use, and Xellia can represent their knowledge, but obviously not knowledge for the rest of the space.

(Pause.)

DR. BADEN: We're looking for the microphone. Thank you for being mobile and later we'll put it in another hidden place.

(Laughter.)

DR. WONG: Hi. Jennie Wong from OSE drug use. We did stratify our data by sales, and I'm not sure if Zelgen [ph] is the same as Xellia, but it does represent -- we have the sales data for about maybe 20 percent, yes.

DR. BADEN: And that was the principal, was that what this company represents is a fraction of the overall sales. And then in addition, there are

a series of groups and are now part of the data because you don't have access to specialty hospitals.

DR. WONG: Yes. But we do have a disclaimer that says just because it's sold from manufacturers through those settings of care doesn't necessarily mean that it was given to patient --

DR. BADEN: Of course.

DR. WONG: They could be sitting on the shelf.

DR. BADEN: We totally understand all the caveats, but I was trying to get us in the right zip code of the amount of use in different sectors.

DR. WONG: Okay.

DR. BADEN: So totally understand the caveats and very much appreciate your clarifying.

DR. WONG: Okay.

DR. BADEN: Dr. Burgess, you have a follow-on?

DR. BURGER: Greg Burger, Stormont Vail Health, Topeka. Did the FDA invite the other companies to present?

DR. NAMBIAR: All manufacturers are informed of the upcoming advisory at the same time.

DR. BADEN: Do you have a follow-on? We're almost to you.

Ms. Hugick, a follow-on?

MS. McVEY HUGICK: Yes. This is Joy McVey Hugick again. I just want to be able to make an informed decision when it comes time to discussion. Because of the absence of the other groups and the absence of data, I'm just finding it hard to get there to know, and maybe that's later when we --

DR. BADEN: And we will come back to that as part of our discussion --

MS. McVEY HUGICK: discussion.

DR. BADEN: -- as how do we weigh the information we have. And part of weighing the information we have is the absence of information. But for now, we are clarifying questions to the industry participants to get as much information as we can, and we very much appreciate your participation.

Dr. Ofotokun?

DR. OFOTOKUN: This is something that it seems like we don't have a good sense of the amount use, but it does appear as some significant amount of use of this drug, both as indicated and off-label use of the product. So it's a polypeptide antibiotic, and there are a number of other polypeptide antibiotics, particularly the polymyxin groups of antibiotics, which are often the last line of drug when we have significantly resistant organism.

I wanted to get from the sponsor, as well as from the agency, if there is any data on cross-resistance between bacitracin and other polypeptide antimicrobial agents.

DR. NAMBIAR: I don't know if we have any particular data to share. I think, as Dr. Baden mentioned earlier, we are not basing this discussion on a lot of data that was submitted to us, so I don't think we have any specific information that we can share.

DR. BADEN: Dr. Green?

DR. GREEN: This is a follow-on to that. I

wonder if the sponsor has current susceptibility data on circulating strains, both for Staph aureus, including MRSA, both CA or community-acquired MRSA, hospital-acquired MRSA, as well as any other organisms. And by current, I would mean like within the last 3 to 5 years.

DR. ANIC-MILIC: It is very difficult to interpret the data when there is no published breakpoints for specific microorganisms, so we are, unfortunately, lacking of this knowledge.

DR. BADEN: Do you have a follow-on? Please?

DR. CALDWELL: This is Michael Caldwell from Marshfield. Are you working to try to establish those?

DR. ANIC-MILIC: Excuse me. I didn't --

DR. CALDWELL: Are you working to try to establish sensitivities and breakpoints for bacitracin and different organisms?

DR. BADEN: I think that's a responsibility of a different group.

DR. ANIC-MILIC: So far, there was no such

initiatives, but maybe triggered by this discussion. Maybe we should try to collaborate with clinical because clinical isolates are the key to assess the susceptibility pattern of some drugs. However, I think that we should not be isolated in this effort.

DR. CALDWELL: Sure. I'm sorry. It sounds like I asked at the wrong time.

DR. BADEN: No, no --

DR. CALDWELL: I'll ask it at the right time.

DR. BADEN: -- your point is a very salient one, but it's for another agency that establishes breakpoints, not companies. There's a group that does that with industry input. And one of the things that come up --

DR. CALDWELL: It would be helpful if they had some information.

DR. BADEN: One of the things that can come up from our discussion is the need for that, and the point that they should think about creating breakpoints if possible, assuming that the

community finds it potentially valuable. But it is beyond any one company to solve that issue.

Dr. Swaminathan?

DR. SWAMINATHAN: I just wanted some clarification from you actually, because it's not clear to me. We're talking about a lot of off-label use, and potential off-label use, and hypothetical off-label use. But you implied that we were supposed to at least initially restrict the discussion to the label indication of intramuscular use for pediatric empyema, et cetera.

DR. BADEN: Dr. Swaminathan, I do not accept your comment because I am us; we are us. I am part of the committee and part of trying to struggle through this information the same as everyone at this table. My understanding from the agency's request to us, in the background documents and particularly in the question as posed in the binder, that is the question before us. And that question is focused on the approved indication.

As we have seen from the presentations and from the discussion, if we accept the sales data on

face value, I accept all of the caveat. There's more than 2 million units a year being used in this country, and as best as I can tell in the last 20 years, I'm not able to get information that it's been used for the indication if you believe the indication is IV or IM.

But we are asked by the agency to evaluate this question based on all the evidence provided to us in the background document, the presentations, and then this discussion, which is why as we further clarify from the agency and our industry colleagues, everything we're asking is of great interest, but the question that we are going to vote on is associated with the specific FDA indication, which does not include irrigation or washing, even though that is of great interest to all of us. That's not the issue at hand. The second question is a broader discussion, but that's not a vote. There are two questions.

DR. SWAMINATHAN: I don't want to be pedantic, but I am a professor, so I would just also --

(Laughter.)

DR. SWAMINATHAN: -- like clarification as to whether the discussion question is saying are there uses for bacitracin IM for other indications, and that would also be a far more restricted question than the use of bacitracin generally.

DR. BADEN: So I guess I will just ask our FDA colleagues to address the intramuscular modifier in question 2 and the specificity of the use of that word.

DR. NAMBIAR: The reason for the languages is the product is called bacitracin for intramuscular injection. The uses could be intramuscular or otherwise.

DR. BADEN: Fine. It's how the regulatory noun is defined.

DR. NAMBIAR: That's how the product -- the product is called bacitracin for intramuscular injection.

DR. BADEN: Thank you.

Back to clarifying questions. Dr. Burgess?

CAPT BURGESS: In your conclusion, you

suggested that the product may be of value for other life-threatening infections. Do you propose to speculate about what other things those might be? We've talked a little bit about MRSA. Any other potential --

DR. ANIC-MILIC: No. This conclusion was directed exclusively to use of bacitracin in approved indication. So considering that there is no new data, we have just data which are historical, but still there is no direct comparison with currently available antibiotics, which are recommended by current guidelines.

In the context of rising multidrug resistance and X-drug-resistant microorganisms, which can jeopardize some patients, which have no other therapeutic solution, maybe because we don't have any additional data that could disturb this risk-benefit balance that has been established in the history, maybe we should think about leaving it as it is. Then as it's already stated in prescribing information, it is intended just in very limited situations; so when the sensitivity to

microorganism is established and there are no other options for the treatment. We think that this part of the conclusion is unchanged because there is no new evidence.

CAPT BURGESS: Can I ask you a quick follow-up? With respect to the approved indication -- and I recognize that this is predominantly for the agency or perhaps others, but to your point, with respect to the approved indication, do you have an opinion about how practitioners should ascertain the susceptibility?

DR. ANIC-MILIC: That is a very good question. The susceptibility should maybe be compared with other antibiotics in the same setting and then see whether there is a difference or no. I really am not a microbiologist. I don't know which techniques could be used. However, I still think if there is a possibility to save some lives, that we should not cease it.

DR. BADEN: Dr. Swaminathan, a follow-on?

DR. SWAMINATHAN: I think there's a problem because there aren't clear EUCAST criteria for

clinical breakpoints for many antibiotics, which are not very commonly used, particularly parenterally. Nevertheless, in studies that have looked at resistance patterns of microbial epidemiology, particularly with respect to bacteria like MRSA or C. difficile, where there's great interest in evolving patterns of resistance, the drug concentrations that are clinically considered relevant, even though there are no official clinical breakpoints, are those that would, by comparison to previous pharmacokinetic/pharmacodynamic data, not be achievable in normal human use; for example, over 100 micrograms per mL of bacitracin. And there is a plethora of data that demonstrates that there has been very rapid evolution of resistance to bacitracin with respect to multiple microorganisms such as Staph aureus, Clostridium difficile approaching 100 percent.

DR. BADEN: Dr. Farley?

DR. FARLEY: Just some additional information. Under the Cures Act, FDA has

authority to recognize standards development organizations, and the recognized organization at the moment is the Clinical Laboratory Standards Institute. As part of preparation for this meeting, we did go through all of the CLSI documents with respect to either methods or breakpoints and cannot find any methods for bacitracin assessment in a laboratory that are recognized by CLSI.

DR. BADEN: And it makes sense to be deferential to a community-accepted standard since every micro lab may have a different way of doing it that becomes very hard to compare. But at this point, there isn't a standard, and I don't think we can then fault the company because the community doesn't have a standard.

I have a question both for the agency and our industry colleagues. Have either groups reached out to pediatric ID specialists, or groups of that ilk, about the use of IM or IV bacitracin for serious infection, so we have some understanding if there is community use in this

setting?

DR. NAMBIAR: We haven't specifically reached out, but we do have a fair degree of in-house expertise in pediatric infectious diseases, and we do have representation on the committee. So we have enhanced membership at this particular representation at this committee with experts in pediatric infectious diseases.

DR. BADEN: I absolutely appreciated, and you have definitely extended the envelope to include experts in the space. My question is a bit different in that I'm more concerned about the 10 or 20 practitioners somewhere in this country with a high level of expertise who are dealing with highly complicated patients, where they have found this to be potentially useful, and just want to make sure that we have attempted to reach out to that community to ensure that if they have a perspective of value, that we're at least weighing it.

DR. NAMBIAR: I think that's a good point. We can certainly take that into consideration. I

think because we felt fairly comfortable with regard to pediatric infectious disease, we didn't reach out to them, but we did reach out to experts in surgical specialties because we didn't have that expertise in-house.

DR. BADEN: Thank you. Dr. Finnegan?

DR. FINNEGAN: This may not be an appropriate question, and it may make some people uncomfortable, but healthcare costs are important. So how much does a unit of bacitracin cost?

DR. ANIC-MILIC: I'm really not assigned to speak about cost of the drug. However, I think that based on literature data, especially in this boundary, which has been mentioned as potentially effective -- in a pancreatic duodenal operation, surgery, that the data is selected because it is so cheap. I think they had mentioned $6 per vial or something like that. So it is not an expensive drug.

Open Public Hearing

DR. BADEN: We will now move to the open public hearing aspect of the committee meeting.

Both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statements to advise the committee on any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. SRINIVASAN: Good morning. Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a master's of public health from Johns Hopkins University. I'm a senior fellow with the National

Center for Health Research, which analyzes scientific and medical data to provide objective health information to health professionals, patients, and policymakers. We do not accept funding from drug and device companies, so I have no conflicts of interest.

We have several concerns about the drug in question today. FDA tells us that intramuscular bacitracin is not used for its approved indication. This is because IM bacitracin has been associated with severe nephrotoxicity in young infants. Fortunately, the guidelines put forth by the American Academy for Pediatrics and the Infectious Disease Society of America for the treatment of Staphylococcus aureus in infants specify other more effective and safer antibiotic therapies, such as penicillin and vancomycin.

The main question posed to the committee today is do the benefits of bacitracin for intramuscular injection outweigh the risks for which its approved indication of the treatment of infants with pneumonia and empyema caused by

staphylococci show to be susceptible to the drug. The simple and straightforward answer is no. This drug is not safe, and approval should have been rescinded decades ago when it was proven unsafe for its indicated purpose.

In looking at the literature on its current use, IM bacitracin is extensively being used off label in a variety of surgical settings to prevent surgical site infections, usually in combination with other antibiotics and antiseptic solutions. But off-label use in a different population for different purposes does not justify its continued presence on the market until those other indications are scientifically proven to have benefits that outweigh the risks. Use of antibiotics without adequate scientific evaluation of safety and effectiveness can lead to preventable harm and also contribute to antibiotic resistance.

The FDA's mission is to protect the public from unsafe or ineffective medical practices, even when it is unpopular to do so. That means holding industry accountable and requiring that companies

meet rigorous approval standards to ensure that medications have benefits that outweigh the risks. Not requiring scientific evidence to keep this product on the market would set a terrible precedent, and other companies would demand the same treatment. We urge the committee to prevent that precedent by voting to rescind approval of IM bacitracin until data are submitted establishing its benefits for another indication. Thank you.

DR. BADEN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. WANG: Thank you, Chair. I'm Dr. Hua Wang. I'm a professor in food science, microbiology, and interdisciplinary nutrition from the Ohio State University. I'm also a former chair in biotechnology and food microbiology of the Institute of Food Technologists and former chair of the food microbiology division of American Society for Microbiology.

I was also the US/UK global innovation

initiative project lead on innovative mitigation of antibiotic resistance in the global ecosystem. I'm a faculty at Ohio State University. My trip is provided by department funds. I don't have any financial conflict to claim.

Today, I would like to share with you the knowledge breakthroughs on food and gut microbiota and an innovative mitigation of massive antibiotic resistance in modern diseases, which is relevant to the discussion today.

According to WHO this year's report listed that antibiotic resistance in the non-communicable diseases is the number 5 and number 2 among the top 10 global public health challenges. As we know, non-communicable diseases right now is responsible for over 70 percent of all the deaths worldwide, and in recent years, gut microbiota dysbiosis is recognized as an important risk factor contributing to diseases such as diabetes and obesity, cardiovascular diseases, cancers, C. diff infection, as well as autoimmune diseases and neurological disorders, et cetera.

In 2016, Dr. Martin Blaser, who is chair of the Presidential Advisory Council, combating antibiotic-resistant bacteria, published a paper in Science. In his paper, he concluded that antibiotic use is responsible for gut microbiota dysbiosis, which is a known causative to many of the modern diseases, as mentioned.

At this point, the primary control strategy for limiting antibiotic resistance as well as gut microbiota dysbiosis is by limiting the use of antibiotics. However, we know that infections happen and that antibiotics are essential. Just pneumonia itself affects 415 million people, and it causes about 4 million deaths annually worldwide. Without proper, prompt antibiotic interference, easy-to-treat bacterial infections can turn into persistent and serious diseases, and biofilms itself are resistant to any treatment, including antibiotics.

Should we use or not use antibiotics? We actually asked even more critical questions on antibiotic resistance and gut microbiota dysbiosis,

and therefore the corresponding non-communicable diseases are inevitable outcomes of antibiotic usage.

With my background in the past 30 years, I've invested my professional life in studying horizontal gene transfer in lactic acid bacteria, rapid detection of micro organisms in foods, hosts, and environmental samples, and we are the group that defined first honeycomb biofilm in the early 2000, using Listeria monocytogenes as the model organisms.

We also conducted studies to understand the mechanism of biofilm formation and horizontal gene transfer. In fact, the honeycomb biofilm structure turned out to be -- was later on recognized as the mainstream term to describe biofilm, replacing mushroom biofilm defined, which was previously using Pseudomonas aeruginosa as the model organisms. This combined background that allowed us to investigate antibiotic resistance in gut microbiota was an unique angle as well as using innovative scope and approach.

In early 2000, we've already switched our focus of studying antibiotic resistant from pathogens to commensal microbiota. For instance, in 2004, we have discovered that the transmission of broad drug resistance, including plasmid, can be facilitated up to 10,000 times by clumping Lactococcal lactis strains, which is commonly used in cheese fermentation, and many retail ready-to-eat deli and restaurant foods carry resistant bacteria, and up to 10 to the 7 copies of antibiotic-resistant genes can be found in a gram of cheese from the retail store. Antibiotic-resistant bacteria further persists even without direct antibiotic exposure.

Commensals, including beneficial bacteria, represent a majority of the microbiota, and these microbiota, instead of the field minor population pathogens, as well as ready-to-consume foods instead of raw meat and poultry, there is the general belief they are in fact the key avenues spreading antibiotic resistance to the general public through food intake.

Now, knowing the real cause to the problem, we were able to develop targeted control strategies. In fact, effective mitigation of the largest antibiotic-resistant gene pool in the food chain, particularly in fermented dairy products, was achieved in just four years with collaboration and support from the industry. The problematic stream was removed from the market, so afterwards, the prevalence and abundance of the resistant gene pools were significantly reduced. This represents the first success in effective antibiotic-resistant mitigation in the food commodity.

When we were studying the impact of food-borne, antibiotic-resistant bacteria of human health, we actually soon recognized that the antibiotic-resistant gene pool developed rapidly in infant subjects in their fecal samples, and that is independent from direct drug exposure, as well as conventional food exposure.

After comparing the amount of antibiotic-resistant bacteria in food they could have been exposed to, as well as a one-time oral

nasal exposure during natural birth versus the antibiotic-resistant bacteria gene pool in the feces, we quickly concluded that the GI tract plays a key role in enriching resistant bacteria even without the presence of any drugs.

So there we ask the real important questions, what are the real risk factors contributing to the problem we're seeing today? The mainstream practice is giving drugs orally, which unnecessarily expose trillions of microorganisms in the gut to the antibiotic selective pressure. Therefore, we decided to investigate the drug administration route, as well as drugs varying in pharmacological properties, particularly excretion routes, as well as drug dosage, drug duration, treatment duration, as well as the food-borne seeds on the impact of gut microbiota, as well as the AR gene pool.

So two drugs that we have tested, one is ampicillin, which is mainly excreted through the renal route, and the other drug that we tested is tetracycline, which has significant excretion

through the bile and gut, even if given by injection. In fact, figure E shows that ampicillin, when it's given orally to mice that are previously inoculated with a small amount of antibiotic-resistant bacteria containing the targeted genes, once receiving oral drugs, very quickly the resisting gene pool in the fecal sample surges to a very high level.

However, the same amount of antibiotics, when given by oral or injection to the same type of mice, then the resistant gene pool in the fecal samples remain pretty much the same as the placebo. If giving the drugs to mice never being inoculated with antibiotic-resistant containing bacteria, regardless of the drugs given by oral injection, the resistant gene pool in the gut remains the same to the placebo.

The difference between injection, as well as oral, the resistant gene pool is about 5 logs. So simply by changing drug administration from oral to injection, we're achieving significant mitigation of the resistant genes in the fecal

samples. When we use tetracycline, we also observe the difference between the oral versus injection. However, the magnitude was less because even by giving injection of tetracycline, part of this still was excreted through the GI tract.

This observation was very clearly demonstrated on the impact of gut microbiota dysbiosis. Figures part c is actually oral administration of ampicillin to the mice, and this is the microbiota profile of the fecal samples. As we can see, after we administer orally the ampicillin, the microbiota changes very quickly. However, D is the one that the same amount of the antibiotics and the same duration of the treatment, the microbiota was very well protected without obvious change.

The same concept was demonstrated with tetracycline treatment as well. Changing tetracycline from oral administration to injection reduced the impact on gut microbiota. However, there are still some impact right there due to the drug excreted to the GI tract.

These data actually illustrated that instead of the use antibiotics, it is the mainstream oral antibiotic administration, as well as drugs excreted through the bio-gut route being the direct drivers of the problems particularly in massive antibiotic resistance and gut microbiota dysbiosis seen today.

These conclusions are supported by historical data on penicillin as well as vancomycin resistance between U.S. and China. I grew up in China, came to the United States about 30 years ago, and penicillin resistance wasn't a massive issue until after the 1990s, however, this problem was much earlier in industrialized countries. This probably correlated very well with the time points that mainstream practice switched from penicillin injection to oral derivatives in these countries.

Furthermore, vancomycin resistance, VRE is already more than 50 percent in clinical isolating United States. However, so far, it is less than 5 percent in China. At this point oral vancomycin is not available in China.

In addition to antibiotics, more than 25 percent of non-antibiotic drugs are now known to impact the gut microbiota as well. So the points that we discussed right here, administration as well as excretion route, probably impact those drugs as well. At this point, we believe that now knowing the real causes to the problems, it makes prompt drug treatment with minimized side effects potentially an achievable goal. If we look at the strains of massive antibiotic resistance versus the rise of those modern diseases mentioned, they had a strikingly similar strain. If the common cause is oral drugs, then that makes sense.

In 2011, we've already presented a special issue organized after our conference sponsored by USD on innovative antibiotic-resistant risk factors and mitigation, and a special issue published by ASM, applauding microbiology -- they presented multiple risk factors contributing to the problems seen today. Finally, it is important to recognize that prudent use of antibiotics does not simply mean ban of, but what, where, and how to use the

drugs

The take-home message is now there are over 250 million antibiotic prescriptions given annually in the United States alone, and mostly probably given by oral, and that impacts every child and a family. We're seeing a massive change of some of those non-communicable diseases from rare incidences now becomes an epidemic in the population. There are four. There is a stressing need for paradigm changes in policies and practices impacting medicine, pharmacy, as well as food/animal production.

This FDA meeting discussing intramuscular injection of an old antibiotic is a critical step forward. However, it is not my background to comment on the drugs, why we pick bacitracin. In terms of the toxicity and potential renal failure in infant subjects, maybe the age of the patients, where to start from, is another thing for the committee to consider.

Overall, we have made this discovery about 8 years ago, but in the past 8 years, this

groundbreaking study has not been broadly known by the society. Our voice has been relatively suppressed and we experienced a lot of difficulties. We shall continue the study to be able to present you with more data and solutions. I would appreciate down the road if federal agencies can provide more support, and this committee, by sharing your expertise, and in terms of discussing and promoting, a potential switch of drug administration away from oral towards other options can be very helpful. Thank you so much for your attention.

DR. BADEN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of all the data before the committee as well as the public comments.

Before we move to the questions -- before we move to further committee discussion, any more

clarifying questions for the agency or our industry colleagues? I will just mention one as anyone else thinks of any.

The agency takes everything we say incredibly seriously. Earlier this morning, there was a comment as to what were the other 7 allergens. It has been investigated, and we have follow up, and I appreciate the agency's diligence on every comment that we make.

DR. JJINGO: I thank Joe for giving me the list.

DR. BADEN: Closer to the mic, please.

DR. JJINGO: Thanks, Joe, for pulling up the information.

Aside from bacitracin, which was the eighth allergen, there was only one other antibiotic that was on this list, and was neomycin. All others were just compounds such as nickel was number 1. But only for our purposes was neomycin another antibiotic. Everything else was not really.

DR. BURGER: Do we have the number that they ranked. I was just, again, curious.

DR. JJINGO: The numbers of all? No. We just wrote up until 8, so nickel --

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I did my own research as well, and that was from a patch-testing panel that was done by the Mayo Clinic, and the average number of allergens tested on the patients was, I believe, 70, and this was the 8th. It was mostly things that are likely for people to come into contact with because it was to evaluate contact dermatitis.

DR. BADEN: Thank you.

Other clarifying questions for the agency or the industry colleagues? Dr. Burgess?

CAPT BURGESS: This is a clarifying question more for surgical consultants that have been invited. We talked a lot about irrigation. Particularly for the orthopedic surgeons, do you have any sense of whether or not bacitracin is used -- incorporated into methyl methacrylate beads or that sort of thing for complicated fracture repairs?

DR. FINNEGAN: Yes. We use spacers or we

use antibiotic beads. The spacers go where the total joint was taken out. The antibiotic beads go down the shaft following an infected rod. It will be a combination of drugs. And as was said before, it's probably historically what somebody's comfortable in using. So yes, it will be used.

CAPT BURGESS: I'm familiar with it with a lot of different agents being used. The question was just, is bacitracin frequently one of them, in your experience?

DR. FINNEGAN: I have no idea.

DR. BADEN: Dr. Meisel?

DR. MEISEL: Steve Meisel. A question for the agency, and it may be unanswerable. It goes back to the -- there's a black box warning that says that bacitracin should not be used with other nephrotoxins such as polymyxin, neomycin, and a pile of others. Yet, it's not uncommon in irrigations to see an irrigation combination of polymyxin, bacitracin, and neomycin.

The adverse event data that was pulled, is it possible that some of the adverse events may

have been because a keyword may have listed polymyxin or neomycin and not bacitracin, even though bacitracin was a component of that irrigation?

DR. NAMBIAR: If you can clarify, you're referring to the FAERS data in particular?

DR. MEISEL: Any of the adverse event data. The 12 cases from PubMed were reported, and it talked about bacitracin. But the other ones on slide, I guess 13, were clearly bacitracin on its own. I'm just wondering if there might have been more or additional cases identified in PubMed or in FAERS because of a quirk in the keywords. It was really a triple antibiotic irrigation with 3 nephrotoxins, but bacitracin wasn't one of the keywords; if something may have gotten missed.

DR. NAMBIAR: Dr. Wassel, who is the review from OSE, can comment.

DR. BADEN: Please state your name.

DR. WASSEL: Hi. My name is Ron Wassel, the safety evaluator with the Division of Pharmacovigilance. No. With the searching

strategy and using the bacitracin term, it would capture all forms of bacitracin that was used, including mixtures.

DR. BADEN: I have another question. As we struggle with this heavily retrospective review, if I'm hearing all the data available to us correctly, is anyone aware of any IM or IV use in the last 40 years?

In looking at it, it looks like in the early '70s, concern arose, and there seemed to be a shift. There have been subsequent discussions and agency reviews. In the pre-digital age, the records are not easily obtainable, but if what I'm hearing correctly from the various agency activities, from our industry colleague, and from what many of us have tried to find on PubMed and otherwise, I can't find any evidence of any -- I will call it systemic use, but IM/IV use in the last 40 years.

Dr. Siberry?

DR. SIBERRY: I'd like to confirm that in my experience and those that I am aware of, that there

is no known use, but also point out that the only known use of IV is inadvertent use associated with possible adverse events. So I just want to make the point that besides the lack of indicated use -- let me finish -- for systemic use, I'm actually concerned that this product poses a risk because its only systemic use has been inadvertent and potentially problematic.

DR. BADEN: I accept the concern of adverse event inadvertent use, but in my mind I'm separating two separate issues, any evidence of efficacy, and I'm in desperate search of any evidence of efficacy, which is separate from any of the safety issues.

Dr. Green?

DR. GREEN: As one of the three people at the table representing the pediatric infectious disease community, because you asked about that specifically, I will say that going only from when I was attending, which is 1989, I have never heard, I've never seen, I've never seen presented, and I've never read of ongoing use of systemic -- that

is IM or IV -- by this product for treatment of the indication pneumonia or for any other. That's an anecdote, but I've been to a lot of meetings, read a lot of papers, and talked to a lot of people over time.

DR. BADEN: Does the agency have any comment? And I'm separating it from Staph aureus. Any systemic use for serious systemic infection in the last 40 years?

DR. NAMBIAR: Our review of the literature did not identify any cases. We did the best we could. Could we have missed a case report or two? We don't know, but to the best of our knowledge --

DR. BADEN: Because that is at the heart of the question that we're being asked. I accept the adverse event issue, and that always has to be weighed in light of efficacy, but we're in search of efficacy.

Dr. Burger?

DR. BURGER: Greg Burger, Stormont Vail Health. We're a 586-bed hospital in Topeka, Kansas with a level 2 NICU. In the 30 years as a

pharmacist practicing, I've never verified an order that went to an infant that was given IM, and I'm sure my other pharmacy colleagues here probably have similar experiences.

DR. BADEN: Dr. Stovall, did you have a comment?

DR. STOVALL: So as one of the pediatric infectious diseases people on the committee, I would say that in my 23 years of experience in 6 different pediatric institutions, I've never seen it used purposefully in a pediatric patient for this indication.

DR. BADEN: Or a systemic for any indication that you're aware of.

DR. STOVALL: Systemic for any indication in a pediatric patient.

DR. BADEN: Yes. Ms. Hugick?

MS. McVEY HUGICK: Joy McVey Hugick again. This is kind of a follow-up on all of the context we've just been given from the experts that deal in pediatrics. Dr. Green had asked earlier if there was precedent at FDA for a similar scenario like

we're experiencing. And I get that you can't know sitting here today what that might be, but to guide us in what we're about to determine, to your knowledge, is it common that drugs stay on the market for decades that aren't being used for the indication?

I just want to provide clarity for myself. I don't want to take something away that might be used and is important in a clinical setting, especially surgically, but if the indications for intramuscular injection for pediatric -- I don't know.

DR. FARLEY: Thanks for the question. So your observation is certainly -- among the antibacterial drugs on the market, this was certainly unusual and what drew this to our attention, and what caused us to feel that it warranted a public discussion regarding benefits and risks. I think it's important today that you are being asked to opine on the benefits and risks of the approved indication, and we would take that back and decide on any next steps, considering that

as well as other information you may suggest.

You may point us in a direction of obtaining additional information, but we're not asking you to opine on an action. We're actually asking you to opine on the benefits and risks of the product for its approved indication.

MS. McVEY HUGICK: Thank you.

DR. BADEN: And I may have missed this. When is the last time an antibiotics indication was withdrawn by regulatory action versus a company withdrawing it?

DR. FARLEY: I don't think we have that information readily at hand.

DR. BADEN: But it's unusual.

DR. FARLEY: This would be unusual, and --

DR. BADEN: Unusual. So what we're being asked is unusual in many ways.

DR. FARLEY: Yes, certainly in the course of postmarketing, if a benefit-risk consideration arises, we would certainly take appropriate action, but that is an unusual event. We agree.

DR. BADEN: Dr. Stovall?

DR. STOVALL: I think the other thing in following, kind of to go along with your question of where we are in this, is that in pediatric infectious diseases, we're used to doing the exact opposite of this. We're used to not having any drugs that are actually approved for our indications, and now we're actually seeing one that we never use that started out for our indication.

DR. BADEN: Dr. Caldwell?

DR. CALDWELL: Is it reasonable to assume that the agency would reach out to the other manufacturers and ask if they have any additional information that we've not been able to --

DR. BADEN: That's a question to the agency.

DR. CALDWELL: I don't know that they ask them that specific question.

DR. BADEN: How hard did you push the other manufacturers for their information as to use and potential benefit?

DR. NAMBIAR: We treated all companies the same, and everybody was offered the same opportunity. No particular invitation was extended

to one person or the other. The same information was provided to all manufacturers, and whoever volunteered is presenting here.

DR. BADEN: Please?

DR. CALDWELL: What was that information? Was it, hi, do you want to come to a meeting, or do you have specific information you might help us with?

DR. NAMBIAR: I think we provided them information that we will be discussing at this certain advisory committee meeting, that there will be discussion around the approved indication, exactly the discussion we're having today. So that's the information we gave them.

We don't solicit information from any one company. In this instance as well, we did not solicit any particular information from the company that presented. I think a more general discussion of this matter will be discussed at a public meeting. These are some of the issues that are going to come up. If you would be interested in participating, you have the option.

DR. CALDWELL: I think I am, like others, struggling with lack of data here and hoping it was in some other place.

DR. BADEN: Along the lines of pushing the agency, this currently has an indication, historical in nature, reevaluated it as the federal guidance has changed. More recently, there are other labeling options such as LPAD or designations of being able to have it available in desperate situations, and you can choose the correct labeling that you have statutory authority for.

Is that something we're allowed to consider? Rather than the historical label, it could be labeled in a way that is a desperate situation. I will use that euphemism and allow you to determine if there's another labeling that could keep it available in the unique situation of serious resistance.

DR. NAMBIAR: So the question we have for you is whether the benefits outweigh the risks. And if your responses is yes, then we would like to hear from you if you have any recommendations

regarding labeling.

DR. BADEN: Thank you. Other clarifying questions?

(No response.)

Questions to the Committee and Discussion

DR. BADEN: If not, then we'll now proceed with the questions to the committee. As we move to the questions to the committee, I would like us to have a little bit of a committee discussion, leveraging each other's expertise as to how to think about this challenging situation. And to start off a committee discussion -- well, I have to do procedural matters.

We'll now proceed with the questions to the committee and panel discussions. I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Before we go to voting on the questions, I would like to have a little discussion among the committee. In particular, I would like to ask my pediatric infectious disease colleague

experts --

In our discussion, we can share our thoughts on what we are struggling with. We may not and should not discuss how we're going to vote. This is to help draw the expertise out of those at the table, so those who are not expert in a sub-area can benefit from the expertise of the committee. But please do not indicate in any way how you are planning to vote on this matter.

From where I sit, one of the things I'm struggling with, as you've already heard, is the issue of efficacy and potential utility. And there I would like to ask my three pediatric infectious disease expert colleagues if you can imagine a scenario where it might be useful to have this available for IM or IV use, given the emerging -- because many of us are aware of emerging antimicrobial resistance, or drug shortages, and our ability to have agents active for invasive infections.

As experts in infectious disease, is it that this is something that hasn't been used for 40

years and will never be used for another 40 years, in which case it speaks for itself as to the risk? On the other hand, might there be scenarios where it could be useful?

DR. GREEN: Dr. Baden, can you please clarify for the pediatric ID experts, you're asking whether this is specific to the question as stated, which is treatment of staphylococcal pneumonia, or are you going beyond --

DR. BADEN: No. I am asking do you as a pediatric infectious disease expert see potential utility? Could you imagine scenarios where IV or IM bacitracin could be useful, not as a irrigation or a wash?

DR. SIBERRY: George Siberry, pediatric infectious diseases. This is something that has never come up since training, even talking to people senior to me, and even practicing in the era of the emergence of resistant bacteria, as an option that would be even theoretically considered. I have not seen this come up as something that would be considered and can't imagine a scenario in

which an alternative, proven, and safe antibiotic option wouldn't be the choice that I would go to. And in most cases, I would have more than one option. Thank you.

DR. GREEN: This is Michael Green. I think one thing that I want the committee to understand is that the pediatric community in general, pediatric infectious disease specialty as a subset of that community in particular, has become very averse to drugs that cause nephrotoxicity.

The use of aminoglycosides has become exceptionally uncommon in our practice, and that's a drug that is used, really, only when other options aren't available. The use of colistin is a last-resort drug for us when you can't use the aminoglycosides, or creative combinations, or newer drugs, or what have you, even if that's off-label use of drugs that are approved for adults and not for children.

I concur with Dr. Siberry that I cannot imagine a scenario, where if there is any other alternative available -- and I can name 7 or 8

different classes that would constitute that variable option -- that I would use this drug.

DR. STOVALL: Stephanie Stovall, pediatric infectious diseases. I would concur with my two colleagues, and also add that particularly in the pediatric population, we're extremely averse to using drugs where we don't have good pharmacokinetic or pharmacodynamic data. And that's one of the concerns with colistin, which is an older drug, which is nephrotoxic, which we're all very unlikely to use unless we're pressed to do so. We don't have good pharmacokinetic data for that drug either, and it's considered extremely risk averse. In this scenario with even less data, I can't imagine a situation where I would choose this drug over, again, 7 or 8 other drugs.

DR. BADEN: Dr. Saine?

DR. SAINE: Hi. Deb Saine. I'd like to pose the question a little bit differently. We've had shortage situations that have affected everything from anesthesia drugs, to opioids, to electrolytes, IV solutions, things that we would

never have dreamed of that we had to find other alternatives.

So posing the question, if a situation occurred where you had no other alternative agents available, would bacitracin be considered?

DR. GREEN: This is still posed to the peds ID folks?

DR. SAINE: Yes. Thank you.

DR. GREEN: I'll take first answer. If you're stating if we have a shortage of penicillins, cephalosporins, glycopeptides, oxazolidinones, quinolones, tetracyclines, and lincosamides -- and those are the ones for have activity against staph -- would I want to reach out to this drug? I think even then I would be reticent, and I would explore still like even perhaps using an aminoglycoside for staph because it does have anti-staphylococcal activity.

Again, the toxicity is real. The use of the drug and how to use it is really no longer known by us, and we don't know how to measure its level or to judge its effectiveness at whether or not even

if the bugs that we're treating are susceptible to it. So I think the answer to your question, even in the extreme, is I would do everything I could possible to not use this drug systemically.

DR. STOVALL: Additionally, I would say that in pediatrics, we're fortunate because our patients typically get better anyway, so source control, particularly as it relates to empyema, would come before using this drug for me.

DR. SIBERRY: Just to concur and just say there are so many alternatives in every situation that you would have to have concomitant shortages across manufacturers, classes, and a huge number of products to even create this scenario.

DR. BADEN: I guess as an adult doctor, I find myself in that exact situation all the time, where I have really resistant bugs and limited therapeutic options. And perhaps the bugs don't transition between environments, but I do find myself being very creative in what to do with, really, resistant bugs, and then on top of that, other sociologic issues as you mentioned. But

that's from an adult perspective.

DR. SIBERRY: So you then thought about using bacitracin in those circumstances, IM?

DR. BADEN: That is not something I have thought about, but the question of should I is a different question that perhaps I should.

Dr. Meisel?

DR. MEISEL: This is Steve Meisel. But in that scenario, you still have to do some sensitivity testing to know if bacitracin would be effective, and we can't do that. We can't do susceptibility testing to bacitracin.

DR. BADEN: There are so many problems. I agree. I concur that the problems are formidable.

DR. MEISEL: So it would just be a guess as to whether bacitracin would be of any value in that dire situation. It would be just a guess.

DR. BADEN: It would be very difficult.

Dr. Swaminathan?

DR. SWAMINATHAN: I do not disagree, but I would like to point out something to clarify a previous discussion about resistance of common

bacteria to bacitracin. Now, while it's true that there are no CLSI or EUCAST methodology or accepted breakpoints, because it really has not been used as a systemic drug in probably 40 years, nevertheless, in studies, peer-reviewed studies as recently as 3 or 5 years ago, there is a wealth of data in journals like antimicrobial agents and chemotherapy, clinical infectious diseases, a variety of top-tier microbiological journals that in highly respected research laboratories have evaluated microbial resistance evolution to a variety of antibiotics.

Another reason that I would not consider this, even as a salvage agent, is because the data by and large indicate that unlike colistin, which may be used as a salvage agent because even carbapenem-resistant bacteria may retain sensitivity to colistin, that is not the case with bacitracin. Empirically, even if I didn't have resistance testing on my patients' isolate because the lab's not allowed to do it --

DR. BADEN: One thing I will say is we

shouldn't be inferring how we're going to vote. We need to stay at the level of information that everyone can use to try and evolve their evaluation.

DR. SWAMINATHAN: Well, you asked whether I would consider this as a salvage agent, and I'm just saying that the reasons that would keep me from considering it as a salvage agent are that, at least even without specific resistance testing, the wealth of the evidence suggests to me that it would not be a good agent in terms of patterns of resistance for bacteria that I'm likely to encounter in practice.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: I'm not a pediatric infectious disease associate, but to answer the question that you asked, could a scenario, any scenario, be envisioned where one might contemplate the use of intravenous or intramuscular bacitracin, the only thing that we haven't talked about so far that I might contemplate would be drug-resistant Neisseria gonorrhea. I would not contemplate that

very long because of the likely development of resistance, to be complete in answering your question.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: I think [inaudible - off mic] -- I just was trying to press our pediatric experts about the same question that you have asked, the scenario where this drug would be useful at all. And the reason I asked -- and I think it's been addressed -- was that we do have drugs like colistin that are nephrotoxic. We rarely use them, but they are on the shelf. And for that one patient for which that drug will be useful, it's there for that one patient.

As an adult infectious disease practitioner, rarely do I use colistin, but occasionally when I have to use it, I'm happy that it's there for that one patient. And I think as I struggle with this, I'm asking myself would there be that one patient for which if bacitracin is on the shelf, it would make a difference in their management?

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: [Inaudible - off mic].

DR. BADEN: Other discussion?

(No response.)

DR. BADEN: I guess one other discussion point that's very, very challenging is not the complete lack of data but near complete lack of data, and that the data we're asked to evaluate are 50 years old, which makes it incredibly challenging. The generation of contemporary data is not incentivized, so the ability for us to have the microdata that was alluded to before, some of the PK data, or the fact that there aren't breakpoint data, speaks to how the community at large is not invested in understanding this, and that puts us in an extremely challenging position, but that is my understanding from everything presented, and the agency obviously is in the exact same position.

So by the transitive property, we appreciate your sharing that with us and in providing all the clarification of what's available. I think the

fact that this meeting is a short meeting speaks to that data frame, not that they're not being as complete as always; it's just these are the realities of the circumstance.

Dr. Weina?

DR. WEINA: I've been quiet, but I just had --

DR. BADEN: I wanted to give you a moment to be able to share.

DR. WEINA: Yes, absolutely.

DR. BADEN: One of the things I like to do at every meeting is I think everybody talks at the meetings. I think that's important to hear everyone's view at the table because I think it's very valuable as we weigh such complicated issues. So thank you for joining this conversation.

DR. WEINA: Thanks for the opportunity. Actually, as I listened to the discussion that's going on, one of the things that struck me was some similarities with quinine and malaria. Of course, we had quinine here in the United States for a very long time, and it was available for the treatment

of malaria, but the use of it was for restless legs syndrome and cramping in the elderly and not for malaria. All of its sales was for leg cramping and restless leg syndrome and never used in the treatment of malaria, and then it disappeared.

Now, whether it disappeared because the agency actually stopped it or because they stopped manufacturing it, I'm not sure. But when eventually somebody came to the agency and said, "Hey, we want to have quinine available for the treatment of malaria," new data was generated for a very old drug that was available for a very long time.

Sometimes if we're not incentivized to provide the data that's necessary to make a good decision on it, maybe the incentive for it is possibly that it's not just available for use off label because you've heard me preach about off-label use all the time; maybe just not have it available for off-label use. We're just going to force the issue that new data comes out. So just a thought.

DR. BADEN: Thank you. If there isn't more discussion for the committee, we will move to the questions, or the question. In answering the question, we'll all vote. Well, I'll read the thing and then give some directive.

We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want. We'll continue in the same manner until all questions have been answered.

What's particularly important about this vote is that the rationale for the key issues that go into your vote, because the agency, as you can tell, is struggling just as much as we are, and I think they want to hear our thinking as to how we're weighing this issue.

The question at hand, do the benefits of bacitracin for intramuscular injection outweigh the risks for its approved indication of the treatment of infants with pneumonia and empyema caused by staphylococci shown to be susceptible to the drug? If yes, please provide any recommendations concerning labeling. If no, please provide your rationale. Please provide any comments or thoughts on your vote.

Are there any questions or comments regarding the wording of the question?

(No response.)

DR. BADEN: If not, then we will open -- I'm sorry. Dr. Ofotokun?

DR. OFOTOKUN: Clarification about this susceptibility. So if we don't have the way to

do -- there's no susceptibility testing and no breakpoint, how do we establish that?

DR. BADEN: That sounds like something for the comments after the vote. What we have now is the state-of-the-art, which is beyond everybody in this room, and I don't think we can change that, but that may be something that we all think is important.

So if no other questions about the wording of the question, then we will move to vote.

(Voting.)

DR. HOTAKI: For the record, the vote for yes is zero; no is 17; and abstentions, 1; nonvoting, zero.

DR. BADEN: Everyone has voted. The vote is now complete. Now that the vote is complete, we'll go around the table, and everyone who voted, state their name, vote, and if you want, state why you voted.

One, what we'll do is we'll go around for this, then for question 2, we'll go around and just have everyone state what they think can be done

next. Shall we start with Dr. Caldwell?

DR. CALDWELL: Michael Caldwell. I voted no, and I voted no because of lack of data, lack of use, lack of way of properly monitoring the use of the drug if we were to use it.

DR. MEISEL: Steve Meisel. I voted no. Thirty-five years ago, this committee, or a version of it, before any of us were born, voted no as well, and there's been no new data since 1982, or whatever that was, to change the dynamic on this.

Observation here, if this drug were a brand new drug submitted today with the data that we have, it wouldn't even make it to this committee. The agency would have asked for substantially more information than we have today on this if this were a brand new drug.

DR. SIBERRY: George Siberry. I voted no; poorly documented evidence of efficacy; real concerns about safety; and ample alternatives that are both efficacious and safe.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. Barb Gripshover. I

voted no, as I believe there are multiple other proven effective antibiotics for Staph aureus and empyema, and the safety concerns of nephrotoxicity and anaphylaxis clearly outweigh any benefits that I see.

DR. GREEN: Michael Green. I voted no. I'll be more succinct because much of my comments I addressed when I spoke in answer to Dr. Baden's question. But I'm unaware of any ongoing use; never heard it; never saw it; never did it; never heard people present it; never heard people publish it since probably back to '83 as a resident.

Clearly, we have lots of alternative drugs. I line listed all the other anti-staphylococcal classes, and essentially it's almost all of them. I don't see any reason to continue approval. And as I mentioned before, the field of pediatrics is really risk averse in general and particularly for nephrotoxicity. I don't think there's any doubt about the nephrotoxicity aspects of this medication, and I suspect it will never be used, for this indication anyhow.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. I voted no, notwithstanding the very real need for options in an era of increasing resistance and the paucity of new drugs that are being brought forward. This has obviously made treating any kind of infection difficult. A major concern I've always had is the off-label use of drugs that are approved for seemingly easy indications. This is a prime example of potential outcomes that you could have with that type of concern.

If the drug is going to be used in a different manner, then data should be brought forward to prove that really does work for that indication. There's no good data provided to show the benefits, or even the potential benefits, as I said, even in the off-label use at this point, and it outweighs any kind of risk of the continued availability of this drug for the indication.

DR. BADEN: Dr. Baden. I abstained, and I often find myself in the minority. I abstained because I think it's somewhat of an unfair

positioning question. There is no one to defend the generics. So if we look at any old drug today through today's lens, we will never have the data of a new application, and it will never have the resources behind it to really work out all of the issues that we've been raising and discussing.

So I share everything that others have said about the lack of data, but that is definitional in this circumstance. And 15 years ago, we would have had the same discussion with colistin, and none of us would have imagined being in the situation where we are today, where I actually use it regularly.

So I guess my imagination about the problems that I'm going to find myself in tomorrow is robust and fearful given antibiotic resistance and the continual emergence. And even though I can't fully appreciate how I would use bacitracin today, in fairness, I've not fully thought about it, but I am worried that I will find myself in circumstances where there are truly resistant organisms that have extremely limited options, whether or not there are

antibiotic shortages, and might this agent have some value.

I'm doing that theoretically. The data are not presented. But this isn't a circumstance where anyone generated data to present to us. Generating the microbiologic data is trivial. Everyone does it, and every time we have something presented to us, there is robust microbiologic data. But that was not the question that was posed to the community. And therefore, the absence of data puts me in an extremely difficult position. That's why I could imagine an LPAD kind of designation where the approval could be modified to one of desperate situation, and we must leave that to the clinicians who find themselves in that circumstance.

In addition, breakpoint data, in vitro data, PK/PD data, actual clinical utility data if anyone ever used it, I think would all be very important. But I don't think that the absence of data -- or I think that the absence of data, because of the way the question was posed, was framed, so there wouldn't be any data. So we're left passing

judgment without data, and the historical data showed some evidence of activity that I'm not quite willing to discard, although it's very hard to interpret.

The issue of toxicity, that goes with anything we use, and therefore, that always has to be weighed. But we are removing the option in a context of increasing antimicrobial resistance, and for that I'm very uncomfortable without compelling data, and the absence of data are not compelling data, in my view.

Dr. Clark?

DR. CLARK: Nina Clark. I voted no for reasons previously stated, based on how the question was worded, a lack of data supporting its use for the stated indication; lack of use over many years; and no anticipated use as stated by our peds ID experts, as well as the absence from multiple society guidelines for using the drug.

DR. FOLLMANN: My name is Dean Follmann. I voted no for many of the reasons that were previously mentioned. There was just no data to

show benefit. There was a known harm for me. I didn't struggle with this at all. I thought it was very clear that in this indication, it was a slam-dunk in my mind.

I thought it was weird that the label said it should be used in organisms that were shown to be susceptible, and yet there are no breakpoints, so that was kind of peculiar, I thought. In the sponsor's briefing, I did a search on randomized trials because I think that is the highest level of evidence that we have, and I found 4 trials, none in the indication for injection. But in 3 of the trials, it trended or was significantly worse on the bacitracin arm than the comparator arm. The 2 trials in and C. diff showed that for colonization -- or negative stool, rather, and one trial in fractures where wound healing was worse in the bacitracin arm.

So there's no evidence in the proposed indication, and in other indications, it's not lining up very well. Also, the fact that multiple societies thought it was not worth doing was

relevant to me, and I thought that was an important point.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted no. I did struggle with the question a lot, but for the indication that for which the drug is approved, I thought that there was not enough data. There was not enough evidence of use. For 40 years, it's not been used for that indication. And there were a number of alternative drugs, a lot and lot, for staph and strep infection.

So I thought that given the lack of data, given the lack of use, and also given the toxicity of the agent, for this particular indication my vote was a no.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: Timothy Burgess. I voted no. The evidence suggesting a benefit was old and of low quality, and the evidence suggesting risk is current and clear, and there are a number of alternatives. I was voting strictly with respect to the question that was asked. I concur with a

number of the comments that Dr. Baden made, and I think we'll have more to say in question 2 about potential future uses.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I voted no primarily for the reasons that have been stated before. I would just like to say I really do appreciate these other concerns about potential use in some situation that we can't envision, as well as some of the off-label uses. But again, to answer this specific question as to whether bacitracin IM, whether the benefits of that for infants with pneumonia and empyema, that question I just did not see any evidence of benefit that's relevant today, and there are known risks, and there are a multitude of alternative agents that have a long track record and are currently very effective.

DR. BADEN: Ms. Krug?

MS. KRUG: Hi. I'm Susan Krug. I voted no basically because I don't like the data. It has not been used. For a person who has had 30 cases of pneumonia starting at the age of 2 months old

with my rare disease, they have pulled drugs out of the back drawers to keep me alive. But this doesn't even have a dosing, and that scares me for the pediatrics. But then again, what you said is so true. I would like it still on the shelf, but I think it needs some modification and more study before it goes back on. That's why I voted no.

DR. BADEN: Thank you. Ms. Hugick?

MS. McVEY HUGICK: Joy McVey Hugick. I voted no for many of the reasons already stated, and I do think it was a simple decision once I thought about it's just for this indication. I don't think we should -- I personally don't feel comfortable recommending a drug stay on the market for desperate situations. I do think that more research is needed and that hopefully the agency will be able to pursue that. But for this question at hand, it was pretty simple based on the lack of data, it's old, it's sporadic, and it's poor quality.

DR. BADEN: Thank you. Dr. Finnegan [sic]?

DR. SAINE: Deb Saine. I voted no. I

appreciated the discussion this morning, and I especially appreciated the opinion of the pediatric ID infectious disease experts. My decision revolved around three topics, one, that there's no new evidence over the past 35 years on safety or effectiveness; two, it's not included in published evidence-based treatment guidelines for this indication; and thirdly, there are a variety of alternative agents available.

I wanted to add an additional comment as well. I recognize that the FDA is not obligated to follow the committee vote, and if the agency decides to keep this indication, I'd like to consider amending the labeled indication to add language such as "when less toxic agents are ineffective or unavailable in the marketplace." Thank you.

DR. BADEN: Thank you. Dr. Stovall [sic]?

DR. FINNEGAN: Maureen Finnegan. I voted no, but it's a very narrow no vote, and it is specifically limited to infants with pneumonia and empyema. My comment would be, coming from a

medical community that looked after Katrina and Harvey, but Katrina in particular, you never know when you're going to be in a situation where you wish you had something.

DR. BADEN: Dr. Stovall?

DR. STOVALL: Stephanie Stovall. I voted no primarily because through the last few decades, we've changed significantly how we approach empyema and pneumonia in infants, and I believe for this indication, we don't have good evidence to show that even had it been effective back in the 1940s, which we can't tell because of how science has progressed over the years since then -- but had it been effective, it probably still wouldn't be recommended today because of how differently we approach pneumonia and empyema in this particular patient population. We have lots of other alternatives available and little understanding as to the benefit of this particular drug in this population.

DR. BADEN: Dr. Burger?

DR. BURGER: Greg Burger. In 1970, this was

a DESI drug, and going back to the 1972 amendment, two letters, we have used it in two instances in the past year, and as may be expected, the drug performed quite well. No other medications presently available would have fulfilled this role since vancomycin is too toxic for use in small children.

We've got lots of alternatives. I think they called vancomycin back then, Mississippi mud. So I think that we've come a long way, and we don't have the data. Thank you.

DR. BADEN: I will summarize the comments from the vote. Sixteen voted no, and the summary of the discussion as I hear it is the question was asked in a focused way. The evaluation by those who said no was specifically related to the question. The lack of new data, clear evidence of toxicity, the emergence of multiple alternative options, societies and guidelines are not favorable to this antibiotic. There's no anticipated use. Overall, the evidence of toxicity outweighs benefit.

On the abstain comment, this is an unfair question because there are no new data by definition, and in that setting, the retrospective scope on most historical approvals would not be favorable. One needs to be careful in that, and there might be ways to frame it for limited options. Many folks commented on the need for additional data such as breakpoints, susceptibilities, PK/PD dosing, so that there are many unanswered questions that would have to be addressed if one were to move it forward.

I've been pointed out I can't count; 17 said no, 1 said abstain, and that's my mathematical error, but that's for the record.

We will now move to the discussion of question 2, and in the discussion of question 2, there are no votes, but we will go around the room and share our thoughts on what is a path forward that could be beneficial.

Are there uses for bacitracin for intramuscular injection other than for treatment of infants with pneumonia and empyema caused by

staphylococci that could be studied? As Dr. Nambiar mentioned, bacitracin for intramuscular injection is framed as how we call the product, not as intramuscular injection, if I interpreted your comments correctly.

So can this agent be used in other ways, and if so, what advice would we give the agency in how to look at that to see if this medication could have a therapeutic use?

We can have a round-robin discussion or it might be easier if we go around the room. If there are discussion points that we want to bounce off of each other, we can do that. Alternatively, we can just start with go around the room and each of us say what we think would be appropriate next steps for the agency to consider.

Dr. Burger?

DR. BURGER: Greg Burger, Stormont Vail Health. Yes, I pondered this for a while and wondered, since we didn't take it off the market back in 1984, that we weren't in any hurry then, and why should we get in a hurry now? My thoughts

are to put a date out there. I don't know what that date would be; 3 years, 5 years, 2 years. I don't know.

You guys that do these studies on drugs, how long does it take to get some data and have a deadline that these companies should come back with information and data to support the use as an irrigation product?

DR. BADEN: Dr. Meisel?

DR. MEISEL: Steve Meisel. I believe the agency did that back 35-40 years ago, and nobody responded. They asked for data on irrigations and other sorts of use, and none of the industry at the time felt that it was in their interest or they could get the data, or whatever the reason was, they didn't do it then. So if they didn't do it, I'm not sure what the incentive would be to do it now.

DR. BURGER: You're dating yourself there, Steve, because I was still in high school then, so I wouldn't have remembered it.

DR. MEISEL: I was 65 years old at that

time.

(Laughter.)

DR. BADEN: Maybe we'll start with Dr Caldwell. I apologize for picking on you. I think it may be better if we just go around the room, and each of us say what it is that we think would be useful as advice to the agency to generate more data if it makes any sense to generate any more data at all. And maybe some of us view this as there is no value, but perhaps there may be value in certain settings, or that value could be defined, and what might that look like as advice to the agency, which obviously would then give advice to industry.

DR. CALDWELL: Just apropos of the last comment, I wasn't aware that in 1984, they asked for -- looking at data for irrigation solutions. I thought it was more related to the primary role, but maybe I misunderstood that. But my thoughts about this is sort of a variation of the old adage. I really didn't want to throw the bathwater out with the baby here.

There are some uses, topical uses for antibiotics, when systemic uses may be toxic but in the situations where they're not absorbed from the periphery. So for non-intracavitary wounds, for instance, this may be very useful. I would really like to know its spectrum. I would like to know its sensitivities.

Irrigation is an important part of surgery. One of the things that I think we need to understand when we're studying surgical site infections is it's surprising to me, given the vagaries that exist there, that any data would come out being conclusive from the studies.

There are over 40 different definitions of infection, essentially none of which have been validated. So that if you look at surgical site infections, the gold standard is not clinical, and most of the studies of surgical site infections go by observers. The gold standard is actually quantitative microbiology of the wound, which obviously is difficult to do, expensive, et cetera.

As a matter of fact, the CDC definition,

1992 definition of surgical site infection, has never been validated. The CDC doesn't even have a standard definition for pus, so we're dealing with -- when all of our outcomes are based on something we can't even define, it's very difficult to find differences when we're looking at things that are used and locations [indiscernible].

I think that it would be very useful if we could understand a little bit more about the dermatitic problems that occur with these solutions because if we were, for instance, to use them for a non-intracavitary wounds, where presumably we would reduce nephrotoxicity, it would be really helpful if we had some way of predicting or have a better idea about the potential for allergic reactions, and certainly anaphylaxis and the like. So those are my comments.

DR. BADEN: Thank you. Dr. Meisel?

DR. MEISEL: Steve Meisel. I'll amend my comment from before. I've been looking back in the FDA slides. It was actually in 1970 that they put out the call and said that applicants had 6 months

to obtain and submit data to support its use for things such as wound irrigations, surgical irrigations, and that sort of thing, and nobody did.

So in 1972, it says here, "reclassified as lacking substantial evidence of effectiveness; no new evidence submitted." That was 1972. So that's been, what, almost 50 years, between then and now, so that's quite a long time.

I recognize that almost all of its use of the parenteral form is irrigations in places like the operating room or clinics and that sort of thing, but it's also apparent that none of the professional groups that were discussed here today, whether it's infectious disease or American College of Surgeons, or the pharmacy groups, or whatever, have felt strongly enough to say that they support its use, that there's enough evidence to support its use.

I don't know how you keep a drug on the market with zero indications. I think this goes back to the quinine question. That was a very good

illustration. The agency I don't think could have a drug on the market that has zero approved indications -- that doesn't make any sense -- just because there's an unapproved indication that everybody sort of likes, but there's no evidence for it.

So if we're going to keep that drug on the market for that indication, then somebody's got to go and do some studies to show that that indication is safe and effective. And particularly in the modern era where we have very different approaches to the prevention of surgical site infections than we did 30, 40, 50, and even 10 years ago, with modern techniques that we have, with all the things that we talked about before and, lots of others, does the added value of an irrigation with antibiotics -- I'm not talking about irrigation of the wound itself with saline for other purposes, but with antibiotics, whether it's bacitracin, cefazolin, or anything else that can be used, whether that would confer additional value to prevent that surgical site infection.

I think it's also important to think about what is the additive toxicity between bacitracin, polymyxin, and neomycin. The package insert has a boxed warning, black box warning, that says don't do that, yet that's what happens almost all the time, is that it seems to be always in a double or triple with one or both of those other agents.

So what is the additional value of adding those two antibiotics? I know there are different theoretical spectrums of activity, some gram negative and some others, but what additional toxicity? When you throw something into a wound, I don't think it's fair to assume that it's not going to be absorbed ever at all. If it's in there, what are the blood levels? How much gets into the system? Over what time course? What are those kinds of pharmacodynamics?

I think the assumption that we're putting into a cavity and it's going to stay there until it sort of dissipates is probably not an assumption that we should accept. I think we should understand what really happens to it. Does it get

into the bloodstream, at what levels, at what rates, and all those kinds of things? And what contribution does that have to any further toxicity and to the problem of antibiotic resistance? Because the more you throw antibiotics in that don't confer value, then the more we have increasing problems with the resistance. So I think that's another element that needs to be studied.

DR. BADEN: We will go around with everyone's comment. If anyone feels rebuttal or new comments emerge that stimulate new thoughts, we'll allow a rebuttal after we're done, if it's compelling.

Dr. Siberry?

DR. SIBERRY: Thanks very much. I am struck by the volume of use of this, not just because it's off label, but also because the professional societies feel like there's no evidence that this practice is adding benefit. But that's the state of medicine sometimes, where we have to just acknowledge where practice is and that people base

their practice on many different factors.

Given that, though, I think that bacitracin for intramuscular use, it's just illogical for it to continue as an approved drug with that name with no indication, and that if there are data, evidence to support a benefit in using it the way that it has had this volume of use, those data should be summarized and made in an application to the FDA to get that indication. And in my mind, that would change dramatically my opinion about the reasonable decision to continue its use. Thanks.

DR. BADEN: If anyone wants to comment on specific areas of high value, where the use might be of great interest, that would be useful. Dr Gripshover?

DR. GRIPSHOVER: I pretty much agree with what's been said. I think that there isn't any good evidence for its current use, which is there is a great deal of, and I'm also struck by how often it's used. But clearly, the practitioners that are using it must feel that there is some benefit. So maybe they would be people to engage

in a study in the sense that it is generic and it might be hard to find a sponsor.

So I do think we need well-designed studies to sort out this issue if it helps in wound irrigation, not just doing it part of a bundle, separating it from just irrigation from irrigation with the drug. And I am worried about the adverse effects, especially the hypersensitivity. I just saw a couple of bad reactions the last week when I was on service, so it isn't benign. Someone had facial cellulitis. I think we need to be aware of those adverse reactions, too.

Then like Dr. Burgess, I wrote down MDR gonorrhea as well when they were listing the other activities, so that might be something we need to keep in the back of our mind.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. With regard to potential alternative use, use and even common use does not imply efficacious use. While the potential role of bacitracin is part of an irrigation or a surgical site infection prevention

strategy, role is being used a lot. We don't really have enough data, I think, to opine on this, and my review of the literature on my own did not provide enough evidence to address this in a meaningful way.

If these potential uses are of interest to the clinical community, it would seem that these uses should be held to the same standard as other products for receiving endorsement for indication. In particular, in my mind, there would need to be an attention to the role of systemic absorption from the various sites of potential use. We know from the peritoneal cavities, there's a lot of absorption. We don't know about those other sites.

I defer to the agency how to operationalize this and whether the product would be available or not during this time period. With regards to systemic use, I don't think likely systemic use in the near future would happen, though it could. If this were to happen, I would think that there might be a way to seek an emergency IND for its use if approval were withdrawn, particularly if these

other trials were going on for product irrigation or other indications at the same time. Thank you.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. It's never fun following Mike Green because he always has these wonderful treaties completely written out, and he sounds so eloquent, and then there's me.

I got to say that one of the things that struck me -- and thank you for your comment, Lindsey, about abstaining and why you abstained. But one of the things that struck me as I was listening to you is that it's a responsibility of the FDA and this committee to help other practitioners who may just pull drugs that are available off the shelf because they're desperate. Other practitioners don't have the luxury that we've had here today to listen to a whole mess of presentations, and then sit there and debate it for awhile, and go, "Hmm, I wonder what's going on," because they're not going to have the time to do that. Usually, it's somebody who they're really desperate about, and they're trying to do whatever

they can to pull off the shelf, and I think it's our responsibility to have those debates and to help the agency make that final decision.

For that reason, I feel very strongly that the agency ought to just pull this thing, if for nothing else to force the issue that new data comes out, and that people will actually set the -- because as long as it's available, off-label use is going to be done. As long as you have it available, why go out and get the data because there's no incentive to go ahead and get the data.

I've been frustrated as a clinician when pushed to the wall to opine on some obscure infection because, "Well, the patient's already been irrigated with a solution that has had various different antibiotics added to it, or mixed into a concrete and used as a filler, or as a salve, and then nothing grew from the wound," but yet the person is still sick.

So opine on what I should do with this patient. And if there's no good data on it and it's just being used, I think that's a significant

problem. So there can be a lot of use without really good reasoning behind it just because it seems to make sense. I think that using it in an irrigation fluid does make sense, but produce some data to show that that actually does make sense.

DR. BADEN: Thank you.

Dr Caldwell, your mic is live, just so you know.

I do appreciate, Dr. Weina, that you listened to my comments. Thank you. I think the community is auto-corrected. Without using it for 40 years, the community has voted with their practice. Though there is fear that there may be wanton, unbridled use systemically, it hasn't happened.

So we must balance the paternalistic concern with the facilitation of the cowboy if one can put that dichotomy out there, and how do we weigh the issue of availability in unique circumstances by experts? Availability of the compound means that that can happen and non-availability compound means it cannot. One may be able to do an eIND, but that

presumes it's still around to do an eIND for.

So I share your concern and the need to balance the paternalistic view with the unbridled use, and that is what the agency struggles with, and we're here advising them.

In terms of how to go forward, I think the community has voted about use in irrigation, not washes, to the point of over 2 million a year. So it's not a trivial use; it is a substantial unbridled use with very controversial data. And there I think that one needs to understand PK because I am concerned by some of the data that shows systemic absorption, and I now wonder if some patients I've cared for had nephrotoxicity because of bacitracin washes that I never thought about in other -- or bacitracin irrigations; I can learn, that I've not thought about as contributing.

So I do think that the issue of PK data -- PK both in sorting out the dosimetry of the drug as well as systemic levels in its current use because there is toxicity we're unaware of that we're scribing to other parts of care because this

is not in our lexicon of things to be aware of. So I think that that is part of the future-looking, improving the safety of this remains in the healthcare marketplace.

If one is to move forward, one needs to develop breakpoints. So pushing our collateral agencies to develop breakpoints for organisms of relevance and not just the gram positives, but perhaps GC. Since people like STIs, syphilis also had susceptibility, so one could imagine other uses, and as resistance emerges, those organisms may become relevant. I think that's a little beyond the scope of the immediate.

I think the scope of the immediate is we need breakpoints for the common organisms. We need to have some understanding of susceptibility data for those common organisms given the breakpoints. We need to understand PK/PD and dosing. We need to understand systemic absorption from irrigation uses. Given that there are 2.3 million -- and I understand all the caveats -- uses annually, one should be able to push for RCTs in that setting to

really define the potential use and how to facilitate those RCTs since this is less likely to be a product with a big ROI.

So having a sponsor invest a quarter of a billion dollar development program seems less likely to me, as opposed to a brand new compound under patent where there is a different horizon. So we need to be careful that the demand is unobtainable unless of course we want this never to be used again.

But I do think that engaging the users -- and engaging the users, I would engage the community to find out if there are others out there who are using it who are experts, and then listen carefully to how they're using it to see how that could be studied. If there aren't, which there may not be, then I would focus on the 2 million uses and say there should be RCTs in this space that are high quality that could actually define use and potential benefit. And I think that's potentially doable.

Dr. Clark?

DR. CLARK: I would say it's also hard to follow Lindsey.

(Laughter.)

DR. CLARK: I just wanted to point out the need for well-performed randomized carefully controlled trials for surgical site infections and prosthesis infections, and doing pharmacokinetics in a variety of patient types, ages, men, women, and critically ill, and surgical patients, and trying to figure out if there are correlates of toxicity such as blood levels.

The one other potential use might be line locks for prevention or treatment of central line-associated bacterial infections if bacitracin penetrates or is active in the presence of biofilms. Then perhaps assessing whether skin testing really is accurate for predicting anaphylaxis since that seems like a big side effect.

DR. BADEN: Thank you. Dr. Follmann?

DR. FOLLMANN: I looked at the question, are there conditions that could be studied, and of

course there could be conditions that were studied as other people on the panel have mentioned. But I don't know that it would really be worth it. I think it's a very difficult path to do studies that would give you evidence showing benefit for this, and I was trying to think what studies would be done.

It's used a lot in irrigation, apparently according to what we've seen today. And yet the one randomized study that was done showed a harm of irrigation with bacitracin versus soap, so that's not a very good sign at all. Another very bad sign is that the multiple societies don't recommend using antibiotic solutions for irrigation. So if I'm a company, I'm thinking, wow, that's kind of not promising at all. So I just don't see where you'd get a successful study out of it, and I don't think it would be a good bet just based on what I've seen today.

The other thing, it was also talked about you had that one special patient who might have a pan-resistant infection, and it's susceptible yet

to bacitracin. But I think such patients are going to be extremely rare, so I don't think you can really study those as well.

So if I'm making a decision, a business type decision as a sponsor, trying to imagine how we would get evidence that would be successful and weigh that against cost. I just don't see a path at all.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: I agree with all that have been said, and I think that moving forward would be difficult but probably not impossible. But should it be possible to move forward, it looks like the community gets use for these products, for surgical site infection, irrigation, and also for topical use. And because there's so much use in that space, that is probably where I would advise the agency to really gather additional data to look not just for the toxicity but efficacy.

The efficacy data in that space is very limited. It's so minimal that it is difficult to make any sense of the data, whether it's beneficial

to use it for irrigation or for topical use, but that is where I would really want to gather additional data. I would do everything that has been suggested, pay attention to toxicity, to safety, to pharmacokinetics, as well as safety.

I would also be interested in a resistance profile of the drug. Also in addition to cross-resistance to using this drug, what harm does it cost to other antibiotics that have similar structure? So those would be areas where I would pay particular attention.

I am a little bit hesitant to say that the drug should be completely pulled in an era where we know that antimicrobial resistance, there's relative shortage of antimicrobial because of resistance. If there's a product that is out there that has not been used for many years, it's possible that a resistance profile may be preserved, and trying to find out that niche, where this drug will be useful, would be something that I would recommend, knowing that this is going to be difficult to do because there's really not going to

be an incentive for any drug company to invest heavily in this product.

DR. BADEN: Thank you. Dr. Burgess?

CAPT BURGESS: In terms of a way forward, the immediate predicate step is to somehow incentivize the comprehensive collection of susceptibility data; a formal breakpoint, yes, but initially, as you said, antimicrobial susceptibility is trivial, in your words.

I would suggest if the question is what could bacitracin be used for, and gonorrhea -- suggests itself because of the emergence of resistance and because it is the subject, at least in part of a national action plan. In addition to the comments that have been made about use in wound irrigation or other surgical site irrigation, I am struck by the volume of use does seem to suggest that -- how it would be resourced is a different question, but at least it seems to be a feasible topic for study.

An additional area would be in the context of what would we lose if the vials were not

available to be pulled off the shelf and reconstituted, and who to ask who might be using this would be individuals caring for the very admittedly niche circumstance, as was alluded to in some of the background cardiovascular device infections.

DR. BADEN: Thank you. Dr. Swaminathan?

DR. SWAMINATHAN: I would like to discuss its potential as a topical agent in irrigation because that's clearly where it appears to be where the greatest off-label use is. Just in mitigation, I think we say wash because our surgeons say, "We'll take them and wash them out" and they say that every day.

DR. BADEN: Your support is appreciated.

DR. SWAMINATHAN: Yes.

(Laughter.)

DR. SWAMINATHAN: But this topic is in many ways the third rail in our interactions with surgeons. Over 35 years, I've learned how to make my peace with this and with the surgeons because otherwise, I wouldn't be able to continue to be an

infectious disease physician. The talk that we've achieved is that they will minimize the use of it where it has clearly been shown not to be particularly helpful. But the surgical guideline -- all these guidelines don't say it should not be used for that purpose. What they say is that it should not be routinely used and that there may be situations where it is beneficial.

As has been pointed out, that has not been proven or disproven, and there are some particularly problematic situations in reconstructive breast surgery, for example, where it is routinely used and where it's high risk of infection.

In addition, most of those apply to prevention of surgical site infections rather than adjunctive treatment of established infection. We have numerous examples of very high-risk surgical situations where there's a high risk of recurrence, and where the recurrence would essentially be life altering or fatal. In those cases, no one is going to tell the surgeon, no, don't do that because the

relative risk of doing that is perceived to be relatively low.

There are also situations I know at our hospitals, that orthopedic surgeons, we do an innumerable number of orthopedic procedures, being in Utah where the skiing is good. They don't use bacitracin very much, but there are things that are in our hospital protocols where we have almost no infection. There's not going to be a randomized prospective trial. They're going to be upset if they can't use bacitracin in circumcision and vasectomies because they just use it topically, every single one.

So I think it is important to see if we can't define better, with careful study design, which local antibiotics are better than others and whether they're better than nothing. That may not be possible. I don't think such studies are ever going to be done for topical use of antibiotics or local use of antibiotics in ophthalmologic surgery because it's established practice and the risks are too great to have a worse outcome than we currently

have. But I think it is possible with non-life-threatening surgeries that are infected or are at high risk for infection. So I think it is important to try to preserve the potential use of this and other antibiotics for those indications.

The other thing I'd just like to address, which is really I think a philosophical argument almost for which there is no right answer, is there are many, many drugs which do not have the indication for which they're used. The most common one that I always think of is the drug that was used for empiric treatment of neutropenic fever, ceftazidime, did not have that indication. Yet, if you had told people that they couldn't use ceftazidime for neutropenic fever, not only would you have been ridden out of town, but patients would have died.

There are many, many, many examples of drugs that we use today that do not have that indication. The only thing is, their primary indication has not been nullified, so a regulatory agency now is in a very unusual position of essentially putting its

imprimatur for an indication in which it no longer believes. And that is a hard thing for a regulatory agency, or for anyone who is supposed to live by the rules and have their rules mean something. And if your rule doesn't mean something because it's not expedient that day, what does the legal system mean at all?

I think that's not a question that I'm qualified to answer, but I think this is a very difficult situation because its primary use has nothing to do with the indication.

I think another thing that FDA should really think about is that because this idea that there might be a niche use or a recurrent use for some of these drugs that are no longer -- are almost considered obsolete, there might need to be an accelerated pathway for resuscitation of those drugs similar to orphan drug mechanisms for emerging threats such as resistant STIs.

I'm not trying to be flippant, but something that used to be very popular, and then was considered obsolete, but then was actually FDA

approved is the leech. And I think we don't want to remove the possibility of creative uses of things that are considered obsolete.

DR. BADEN: Thank you. Ms. Krug?

MS. KRUG: I think there is use for it having a lot of orthopedic surgeries, but I would like to have more research on this. I just don't want doctors taking it off the shelf and throwing it in. I have had anaphylactic shock 3 times since the surgery, and they go, "Oh, it's combination of one of the three antibiotic washes we gave you." They have no idea what it is.

So I do think that you need for this drug -- it should be available because I am allergic now to so many drugs that it may be the only thing that keeps the staph off me, irrigation, not wash. But there has to be some research; it just can't be randomly used. I've had 31 orthopedic roddings, and I have not had an infection, staph or anyways. They have used this drug topically on top of the sutures, and maybe that did it; maybe the washes have done it. I've

also had dermatitis, that I've had blisters, and I was inside my head because of this drug.

So you need to do studies, but should it be taken off? I don't believe so, totally. Thank you.

DR. BADEN: Thank you. Ms. Hugick?

MS. McVEY HUGICK: I don't envy FDA. It's such a tough situation because just because people are using it doesn't mean it's useful. And it's hard for organizations to make recommendations and guidelines with the lack of data.

So where to go from here? Well, obviously, it's being used, 2 million uses a year. So that's not a question; it's definitely being used. What I would suggest is taking a pulse check where it's being used and find out before you insist on studies, because I think more research is needed, but like Dr. Follmann was saying, maybe not. But before you can do that, I think taking a pulse check, talking with your partners, and finding out in operating rooms where it is being used and is effective, potentially. But do we really know

that? Well, it might have been one of the drugs in the mix of things that we use. But do we know that it was that drug that made a difference? I don't know. I think that's where you kind of have to start.

DR. BADEN: Thank you. Dr. Saine?

DR. SAINE: Hi. I'll be somewhat of a purist here and go back to the question that says are other uses that could be studied? I believe the answer's yes. I think the primary area that we've seen of interest is topical use for surgical site infection prophylaxis.

For me, I practiced in different regions of the country, different types of hospitals. It's very common to see bacitracin-containing irrigation solutions for the OR to vary depending on the area of the country and depending on the type of organization. It depends on where the surgeon trained. It can depend on individual experience in any number of factors.

So I would like to see more rigorous comparative studies that address things like

specific dosage, concentration of the solution, route used or method of administration, the duration, timing, volume, and so on, with some controls or some assessment of use or not use of systemic antibiotics and controls for other standards of practice for infection prophylaxis as well.

In addition to that, another area of interest would be given the safety profile of this drug, human factors studies to avoid inadvertent systemic administration. Thank you.

DR. BADEN: Thank you. Dr. Finnegan?

DR. FINNEGAN: So the cowgirl is very proud to give her opinion. I think there are a couple of things. First of all, I think one of the reasons for the lack of data is because this medicine has been around forever, so no one realized that there was actually a question about whether it worked or not. I think that's number one.

Number two, in 1970, early 1970s, very few total joints were done. They were done mostly on the elderly and people with very little morbidity.

That is not the problem now. BMIs of 50 are getting total joints, which is a totally different question. And in the 1970s, we barely knew how to treat open fractures, and internal fixation was rarely done. Gustilo's classification came out in '76, so I think that the 6 months that the FDA gave was to the wrong audience, and therefore there needs to be more than 6 months to a different audience, which would be more interested.

As far as Jeff Anglen's study is concerned, he was actually looking at bacitracin versus the soap on implants, which is getting rid of the biofilm, which is an entirely different thing than washing out and a wound.

The other thing is that I think actually in neurosurgery, there may be some data, and there is data that bacitracin does not cross the blood-brain barrier, so I'm assuming it also doesn't cross the brain-blood barrier. So that might be one of the groups to look at, as well as plastics. Also, it's my understanding that ENT uses it in nasal surgery for washouts, so I think those are groups that have

a great deal of experience in very specific instances that might be worth reaching out to. And that's it.

DR. BADEN: Thank you. Dr. Stovall?

DR. STOVALL: Stephanie Stovall. In the day and age of antimicrobial stewardship, I think it would be interesting to try to push looking at certain types of infections like Dr. Finnegan mentioned, the ENT category or CNS category, to see if treatment of these deep spaces, potentially, could be used as an antibiotics sparing tool that might drive the public to be more interested in actually studying this drug if you present it that way.

The other thing that I'll say that I feel strongly about is that while we have good evidence that it doesn't cross the blood-brain barrier, for instance, we don't have good evidence that the other barriers are not compromised. In fact, we have some that is contrary to that effect. I think we have to be extremely focused on making sure that the continued use is actually safe. So I think

safety needs to be the primary focus of your further research.

DR. BADEN: Dr. Burger?

DR. BURGER: Greg Burger. I have one more comment, which goes on with human factors engineering. If we are going to go forward with this product as an irrigation solution, it needs to be out of the vial. I would be amiss as a medication safety coordinator to say you're setting people up to draw that up into a syringe and give it to someone systemically when the route is primarily being used as an irrigation now. So we have to change the way it's delivered. Thank you.

DR. BADEN: Thank you. To summarize the big themes that I heard, the potential niche that this may be beneficial needs to be defined both in vitro and in vivo. A challenge in moving forward is it may be standard of care to use it in certain situations, and therefore, despite our discussion about lack of evidence, if one offers a study that goes against the standard of care that creates certain challenges that have to be thought about,

the incentives have to be aligned appropriately to be able to achieve the objective.

RCT data should be generatable given the volume of use, and if that volume of use is better defined, then those groups can be targeted and properly engaged. Human factors and the safety and better defining the safety can be augmented, and some thought that it just may be undoable given the state of the data and the lack of logical incentives.

Any other comments from committee members to the agency? Dr. Meisel?

DR. MEISEL: Steve Meisel, a couple of things I thought of here as we were going around the discussion. I know this is a very difficult task, the idea of having a drug on the market that has no primary indication. I don't know how the agency deals with that.

There is an unintended consequence here that I think we need to be cognizant of. Let's assume the agency goes down the path of withdrawing the drug altogether because there's no indication for

it anymore, but the folks who use it for irrigation still believe in using antibiotic irrigations. Well, then what's their alternative? They'll be using more beta lactams. They'll be using more whatevers with that. And what's the impact of the increased exposure of those on antibiotic resistance and other kinds of avenues?

I think that's an unintended consequence to where -- I believe it should be withdrawn. Don't misunderstand me. I think the data suggest that it really shouldn't be there, no safety efficacy data for really anything. But I'm cognizant of, and I think the agency needs to be cognizant of, the unintended consequences if we don't change people's beliefs that antibiotic irrigations have value in this space. So I think that's an important thing to keep in mind.

The other thing that occurs to me is that although we're talking here about the injectable form, parenteral form of bacitracin, a lot of what we discussed about efficacy and does it really even work against all these organisms applies to the

topical. Topical bacitracin is used all over the place; it's over the counter. But is there any evidence that it actually does anything for anybody?

I think that's beyond the scope of today's discussion, but I think it's a logical next step for the agency to be thinking about. If we take these steps with the parenteral bacitracin, what does that mean for topical bacitracin?

DR. BADEN: Dr. Finnegan?

DR. FINNEGAN: Just to be a surgeon, didn't bacitracin come from the open wound of a kid? Isn't that how they figured it out that it was actually a medicine?

DR. BADEN: Tracy was the patient in New York.

DR. FINNEGAN: So it obviously works topically. I think bacitracin was discovered when this woman scraped a kid's knee wound, and pulled out the bacteria, and discovered it produced this material.

DR. BADEN: Yes, it affected the growth of

Staph aureus done at Columbia in New York.

Do our industry representatives have any comments given the nature and complexity of the discussion? If you can speak in a microphone.

DR. EICHMANN: Ed Eichmann. We'll take all this advisement so far and bring it back to our colleagues back in the office. And like it brought up, we have to look at the economics of running a study, the possibility of doing a study, and the approval process of doing the study, and all this will be evaluated when we have a chance to talk with the agency.

DR. BADEN: Thank you.

Any final comments from the agency?

DR. NAMBIAR: Thank you, Dr. Baden. On behalf of the division and the office, I want to extend my thanks to all of you for participating in today's meeting. I understand some of you were here yesterday as well, so it's been a long day and a half.

So thank you very much. I think the feedback we've received is very useful and a very

robust discussion. So we'll take all this back, and it will inform us in our decision-making as we move forward.

I also want to extend my thanks to our colleagues in the Office of Surveillance and Epidemiology and the review team for all the work that they did. Safe travels, and I'm sure we'll be seeing you soon. Thank you.

Adjournment

DR. BADEN: Thank you, and the meeting is now adjourned.

(Whereupon, at 1:02 p.m., the meeting was adjourned.)