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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

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Lauren Tesh Hotaki, PharmD, BCPS**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

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8 **ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS**

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10 **Lindsey R. Baden, MD**

11 *(Chairperson)*

12 Director of Clinical Research

13 Division of Infectious Diseases

14 Brigham and Women's Hospital

15 Director, Infectious Disease Service

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17 Associate Professor, Harvard Medical School

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11 Translational Science

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5 Sr. Vice President

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17 Medical Director, Pediatric Antimicrobial

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19 Medical Director, Infection Prevention/Epidemiology

20 Golisano Children's Hospital of Southwest Florida

21 Lee Health System

22 Fort Myers, Florida

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4 Office of Antimicrobial Products (OAP)

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10 Division of Anti-Infective Products (DAIP)

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13 **Thomas Smith, MD**

14 Clinical Team Leader

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1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Lindsey Baden, MD	13
5	Conflict of Interest Statement	
6	Lauren Tesh Hotaki, PharmD, BCPS	18
7	FDA Opening Remarks	
8	Thomas Smith, MD	22
9	FDA Presentation	
10	Bacitracin for Intramuscular Injection	
11	Labeled Indication and Current Uses	
12	Caroline Jjingo, MD, MPH	30
13	Clarifying Questions	45
14	Industry Presentation - Xellia	
15	Safety and Effectiveness of	
16	Bacitracin for Intramuscular Injection	
17	Tatjana Anic-Milic, MD	66
18	Clarifying Questions	92
19	Open Public Hearing	120
20	Questions to the Committee and Discussion	151
21	Adjournment	221
22		

1 P R O C E E D I N G S

2 (8:30 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

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

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

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

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

22 DR. NAMBIAR: Good morning. Sumathi

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

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

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

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

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

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

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

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

1 infectious disease.

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

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

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

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

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

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

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

22 CAPT BURGESS: Tim Burgess, adult infectious

1 diseases, Uniformed Services University School of
2 Medicine, Bethesda.

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

6 MS. KRUG: Susan Krug, patient
7 representative.

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

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

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

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

22 MR. BURGER: Greg Burger, medication safety

1 coordinator, Stormont Vail Health, Topeka, Kansas.

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

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

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

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

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

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

11 **Conflict of Interest Statement**

12 DR. HOTAKI: The Food and Drug
13 Administration is convening today's meeting of the
14 Antimicrobial Drug Advisory Committee under the
15 authority of the Federal Advisory Committee Act of
16 1972. With the exception of the industry
17 representative, all members and temporary voting
18 members of the committee are special government
19 employee or regular federal employees from other
20 agencies and are subject to federal conflict of
21 interest laws and regulations.

22 The following information on the status of

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

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

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

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

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

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

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

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

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

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

11 DR. BADEN: Thank you.

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

14 **FDA Opening Remarks - Thomas Smith**

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

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

4 Bacitracin is a complex polypeptide derived
5 from cultures of *Bacillus subtilis*. The major
6 component of it is bacitracin A. It's active
7 in vitro against a variety of gram-positive and a
8 few gram-negative organisms. The drug is assayed
9 against the standard activities expressed in units
10 with 1 milligram having a potency of not less than
11 50 units. It's available as a sterile powder in
12 vials containing 50,000 units, and it's currently
13 marketed under several approved abbreviated new
14 drug applications.

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

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

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

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

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

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

9 FDA contracted with the National Academy of
10 Sciences and National Research Council to make the
11 initial evaluation of the effectiveness of products
12 that have been approved only for safety between
13 1938 and 1962. The NAS-NRC created review panels,
14 and these panels submitted reports to FDA in the
15 late '60s and early '70s. FDA reviewed and
16 reevaluated the panel findings and published its
17 findings in Federal Register notices. The
18 administrative implementation of these reports was
19 called drug efficacy study implementation or DESI.

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

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

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

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

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

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

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

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

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

22 Following the 1984 advisory committee

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

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

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

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

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

12 Thank you.

13 DR. BADEN: Thank you, Dr. Smith.

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

16 **FDA Presentation - Caroline Jjingo**

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

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

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

1 are currently no FDA recognized breakpoints for
2 bacitracin.

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

11 We conducted a literature review looking at
12 the uses of bacitracin in infants with
13 staphylococcal pneumonia. We retrieved a total of
14 4 articles published between 1957 and 1972. No
15 relevant publications were identified in our search
16 after 1972. All 4 publications, which I will go on
17 to summarize, provided very limited and largely
18 descriptive information on the use of intramuscular
19 bacitracin for the treatment of staphylococcal
20 infection in infants. Bacitracin was administered
21 intrapleurally in neonates with empyema.

22 I wanted to discuss now the first two

1 articles, both of which were published in the late
2 1950s. Just to provide you with a background, this
3 was in a setting where there was increased
4 staphylococcal infections in parallel with a
5 growing penicillin resistance, and staph pneumonia
6 was found in early infancy and can be fatal in that
7 particular demographic.

8 Koch et al. in 1957 published a
9 retrospective, single-center case series of
10 480 pediatric patients with various staphylococcal
11 infections in children between the ages of 2 days
12 old to 15 years old. Eighteen percent were
13 reportedly less than 2 months of age. The number
14 of children with staphylococcal pneumonia treated
15 with bacitracin and their clinical outcomes was not
16 described, and bacitracin was used in conjunction
17 with chloramphenicol in this particular study.

18 Pryles et al. in 1958 published a
19 retrospective case series of 24 patients, all of
20 whom had staph pneumonia. They ranged from the age
21 of newborn to 42 months. Nineteen of the
22 24 patients had complications of pneumonia with

1 empyema. All patients were given parenteral
2 antibiotics, and bacitracin in 7 patients who had
3 empyema was instilled intrapleurally at a dosage of
4 5,000 to 10,000 units and given over 2 to 8 days
5 without adverse outcomes. The authors recommended
6 local administration in severely ill infants with
7 massive empyemas. However, they warn that
8 considerable caution should be exercised while
9 doing so. No nephrotoxicity was observed in the
10 7 patients.

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

1 Geley et al., the final publication,
2 published a series of 273 cases from 1954 through
3 1956 and 1957 through 1970. 152 of these patients
4 had Staph aureus. A singular reference is made to
5 bacitracin used in combination with neomycin, which
6 was described as quote/unquote "excellent local
7 antibiotics for installation into the pleural
8 cavity in neonates and infants with empyema." It
9 was unclear, however, how many children in this
10 case series received this drug combination, as well
11 as the clinical efficacy or microbiologic outcomes
12 in response to this combination therapy.

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

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

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

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

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

1 for injection is largely being used in adult
2 patients.

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

12 Please note that the total percentages
13 across locations is greater than 100 percent, as
14 multiple administrations across all locations were
15 captured. Patients who received more than
16 1 administration of bacitracin were counted more
17 than once.

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

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

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

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

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

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

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

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

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

4 Now we'll go on to discuss bacitracin
5 related safety concerns, which there were primarily
6 three: nephrotoxicity, much of which was
7 characterized in the early literature from the
8 1940s to 1950s, and it was characterized by renal,
9 tubular, glomerular necrosis, proteinuria,
10 albuminuria, elevations in BUN, and decreases in
11 renal function. Hypersensitivity has also been
12 quite well characterized, including anaphylaxis.

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

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

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

7 Meleney et al. in 1949, in a case series of
8 270 patients, largely surgical who received 50,000
9 units of bacitracin every 6 hours, administered
10 locally or systemically, reported also experiences
11 where albumin appearing in urine 2 to 3 days after
12 the initiation of bacitracin treatment was
13 observed. Active urine sediments on urine
14 microscopic analyses, namely urine casts, were
15 observed; elevations in blood nitrogen or uremia;
16 declines in glomerular and tubular filtration; and
17 also specific gravity.

18 Miller et al., again in their 1950
19 publication, also noted that 148 patients with
20 early syphilis received parenteral bacitracin. All
21 148 developed proteinuria and casts during the
22 course of therapy. Hematuria was rare.

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

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

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

1 standing for FDA Adverse Events Reporting Systems,
2 and this search was through December 12, 2018 and
3 included any reports of parenteral use of
4 bacitracin through such administration through
5 intramuscular, intravenous, or intraperitoneal
6 administration. They identified a total of
7 35 cases: 24 cases where bacitracin was used as an
8 irrigation solution and 11 cases in which
9 bacitracin was used intravenously.

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

22 In summary, there are several take-home

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

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

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

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

11 **Clarifying Questions**

12 DR. BADEN: Thank you, Dr. Jjingo.

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

1 I think Dr. Green has first question.

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

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

18 DR. BADEN: Dr. Meisel?

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

1 question about the age and location of the use.

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

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

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

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

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

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

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

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

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

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

14 DR. WONG: Yes, that's correct.

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

17 Dr. Follmann?

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

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

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

7 Does that help clarify?

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

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

15 DR. FOLLMANN: I see.

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

18 DR. SCHUMANN: Right. It's --

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

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

1 by the statute.

2 DR. FOLLMANN: Okay.

3 DR. SCHUMANN: Is that helpful?

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

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

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

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

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

3 DR. FOLLMANN: Thank you.

4 DR. BADEN: Did you have a comment?

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

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

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

17 DR. BADEN: Dr. Finnegan?

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

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

4 (No audible response.)

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

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

11 DR. FINNEGAN: Any detail.

12 DR. JJINGO: -- detail.

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

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

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

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

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

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

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

17 Is that correct?

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

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

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

8 DR. JJINGO: That's correct.

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

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

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

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

8 DR. BADEN: Okay.

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

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

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

17 DR. BADEN: From that way.

18 DR. SMITH: -- purpose.

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

22 DR. SMITH: We believe that's correct.

1 DR. BADEN: Dr. Burger?

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

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

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

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

14 DR. BADEN: Through the dermatologic allergy
15 community.

16 Dr. Green?

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

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

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

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

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

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

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

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

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

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

21 DR. SCHUMANN: Yes.

22 DR. BADEN: Dr. Ofotokun?

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

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

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

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

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

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

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

1 close to what you would get with parenteral
2 administration.

3 Tim, do you want to comment?

4 DR. BENSMAN: Tim Bensman, clinical
5 pharmacology, FDA. Yes, there was a paper looking
6 at intraperitoneal lavage solution, about 50,000
7 units of bacitracin in 200 mLs/NS. Dwell times
8 were 2 and 5 minutes, and then they suctioned it
9 out. Serum levels were approximate 2 IM
10 50,000-unit doses.

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

20 We have a few more questions. Dr. Follmann?

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

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

9 DR. BADEN: Dr. Caldwell?

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

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

1 We don't do laundry.

2 (Laughter.)

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

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

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

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

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

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

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

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

1 fees, travel expenses, honoraria, and interest in a
2 sponsor, including equity interests and those based
3 upon the outcome of the meeting.

4 Likewise, FDA encourages you at the
5 beginning of your presentation to advise the
6 committee if you do not have any such financial
7 relationships. If you choose not to address this
8 issue of financial relationships at the beginning
9 of your presentation, it will not preclude you from
10 speaking.

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

14 **Industry Presentation - Tatjana Anic-Milic**

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

1 meeting to participate in discussion about
2 bacitracin efficacy and safety.

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

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

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

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

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

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

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

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

1 hypersensitivity is contraindicated for
2 intramuscular administration of bacitracin.

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

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

22 Regarding the different shapes and colors on

1 this display, the small gray circles represent the
2 studies in which titles or further details have
3 been revealed. For the light blue circles, which
4 varies in size, for the smallest circles, these are
5 representative of studies which are just case
6 reports or studies of case series up to 10
7 patients. Following by the size, there is
8 noncomparative studies comprising 10 to 50, 50 to
9 100, or more than 100 patients.

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

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

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

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

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

1 market.

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

11 There were also some trials and bacterial
12 enteritis, and the prominent use was in '80s and
13 '90s for a surgical site prophylaxis by the oral
14 route in terms of colorectal surgery in regard to
15 the colonization, and also with regard to the
16 contamination in neutropenic patients because of
17 prevention of sepsis originating from the gut.

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

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

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

9 Koch and Donnell in the late '50s described
10 treatment options they used in the treatment of
11 staphylococcal infections in infants, stating that
12 bacitracin is used in combination with
13 chloramphenicol in the most serious infections, in
14 23 patients where only 2 children died of empyema
15 and pneumonia, probably at least in one child due
16 to a late diagnosis than on treatment failure.
17 Authors concluded that bacitracin belongs to the
18 treatment of choice in Staph aureus infections,
19 particularly when a high rate of penicillin
20 resistance was noted. The majority of patients'
21 isolated strains, 92 percent were resistant to
22 penicillin and 75 percent were resistant to

1 tetracycline.

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

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

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

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

7 Corroborating clinical data in adults
8 complement for this condition in infants. There is
9 a case report of a 62-year-old man who has been
10 treated successfully with bacitracin, supported by
11 lung penetration of bacitracin in lungs, based on
12 successful treatment of lobar pneumonia in adults
13 in the second study, where 14 patients have been
14 treated with bacitracin, and cure rate raises to
15 86 percent. The key pathogens identified were
16 streptococcus pneumoniae and hemolytic
17 streptococcus or both. This study doesn't show any
18 specific MIC values, but implies that sensitivity
19 of these pathogens have been confirmed.

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

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

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

14 In a study of Geley, there the mortality
15 rate decreased from 11.8 in historical control to
16 5.7 after treatment with bacitracin, which is
17 almost a double decrease in mortality, which is a
18 very important endpoint. Willital and co-authors
19 reported a decrease in septicemia rate, which is
20 almost 3 times lower than a historical controls,
21 reducing from 65 percent to 21; and also a decrease
22 in abscess formation and re-surgery need, as well

1 as consequent fibrosis, which is also reduced from
2 77 to 21.

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

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

1 satisfactory efficacy could be attractive options
2 for local treatment.

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

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

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

1 recommendations. There are three surveys that we
2 succeed to capture from the literature. The first
3 one was performed in 984 orthopedic surgeons, and
4 the second one in 186 orthopedic surgeons, and the
5 third one was in operating room nurses. In all
6 surveys, it was recognized that at least 16 to
7 20 percent of users in clinical settings used
8 bacitracin or similar antibiotic for wound
9 irrigation despite lack of recommendation and major
10 guidelines.

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

22 What are the most often used ways of

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

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

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

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

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

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

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

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

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

22 There are also some additional studies in

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

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

15 DR. BADEN: You have 10 minutes.

16 DR. ANIC-MILIC: I'm sorry?

17 DR. BADEN: Ten minutes.

18 DR. ANIC-MILIC: Okay.

19 DR. BADEN: Thank you.

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

1 occurred across the studies. It ranges from 50 to
2 2000. Also, other variables have to be taken into
3 account in terms of duration of irrigation, local
4 susceptibility, or also a need for gram-negative
5 coverage.

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

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

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

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

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

22 The second study was pretty much in the same

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

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

17 There was one case report in which a
18 25-year-old patient with leukemia developed VREF
19 bacteremia, and after all treatments with
20 tigecycline, rifampin, quinupristin-dalfopristin,
21 linezolid, and ampicillin, which was successful,
22 the administration of bacitracin solved and cleaned

1 the gut within 48 hours.

2 Switching to bacitracin safety, bacitracin

3 is over 70 years in the clinical field.

4 Intramuscular use was ceased in the '60s due to

5 nephrotoxicity. In '78, Eichenwald reported that

6 adverse renal effects were rarely found when

7 bacitracin was used in early infancy, even claiming

8 that it is better tolerated than vancomycin in this

9 early age.

10 Local administration, especially surgical

11 wound irrigation for surgical site infection

12 prophylaxis and treatment, gained, again,

13 acceptance based on research interest that is

14 obvious from published data. Widespread use of

15 topical bacitracin product for the treatment and

16 prevention of superficial infections caused a

17 hypersensitivity problem. I have a date, that

18 dated in 1992, bacitracin was 7th, although

19 Julie [ph] pointed that in later ages it became

20 8th. This is probably because of widespread use of

21 topical bacitracin. And just a brief hover over

22 DailyMed, it can be identified in more than 500

1 bacitracin-containing products.

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

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

22 The history of skin reaction has been often

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

6 By searching FAERS data, we have identified,
7 since inception of FAERS in 1969 through the end of
8 2018, 637 reports related to bacitracin. Out of
9 them, 216 events were classified as serious. From
10 these reports, we just picked up reports based on
11 literature data, which are most prominent after
12 intramuscular or local administration and are most
13 important. We have identified 37 reports of
14 anaphylaxis and 9 reports of renal or urinary
15 disorders.

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

1 bacitracin remains unchanged.

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

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

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

1 timelines, and thank you for your attention.

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

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

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

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

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

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

21 **Clarifying Questions**

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

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

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

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

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

17 Dr. Finnegan?

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

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

1 will be appreciated.

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

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

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

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

1 MRSA has been identified in 4 to
2 5 [indiscernible] patients, and success was 58
3 percent success rate. MRSA has been identified in
4 5 patients, and the success rate with this
5 combination, it was not monotherapy; it was
6 20 percent only.

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

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

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

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

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

3 DR. ANIC-MILIC: Which indication?

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

6 DR. ANIC-MILIC: Slide 20?

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

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

13 DR. BADEN: Dr. Swaminathan?

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

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

22 DR. SWAMINATHAN: I'm referring data in

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

3 DR. ANIC-MILIC: Okay. Thank you.

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

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

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

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

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

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

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

17 DR. BADEN: Dr. Meisel?

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

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

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

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

16 This bundle, bundle which contains
17 bacitracin in comparison with no perioperative
18 bundle, beared success. So the infection rate was
19 11 percent in comparison with control, which was
20 22 percent.

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

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

3 DR. ANIC-MILIC: Yes.

4 DR. MEISEL: -- versus basically nothing.

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

6 DR. MEISEL: Yes. Thank you.

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

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

12 So a different line of question. The issue
13 of systemic use intravenous/intramuscular, in the
14 5 years that you all have been marketing this
15 product, are you aware of systemic use by
16 intramuscular IV use for serious invasive
17 infection?

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

22 DR. BADEN: Sure.

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

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

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

17 DR. BADEN: Thank you.

18 Dr. Burgess, do you have a question?

19 (No audible response.)

20 DR. BADEN: Dr. Caldwell?

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

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

6 DR. ANIC-MILIC: That is interesting because
7 when comparing vancomycin and bacitracin in the
8 treatment of C. diff associated diarrhea, the
9 clinical response was similar, and the relapse rate
10 was similar as vancomycin. However, when
11 monitoring -- so if we talk about the follow-up, we
12 can measure it by relapsed rate, which was I think
13 33 versus 20 percent baci versus vanco, which was
14 statistically insignificant.

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

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

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

9 DR. BADEN: The flora.

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

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

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

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

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

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

9 DR. FINNEGAN: It is a follow-on on the
10 vancomycin/bacitracin events. Even though her CDC
11 statement on slide 12 says that the CDC recommends
12 no antibiotic powder in wounds that in fact is not
13 exactly being followed, there are two studies in
14 2018, one in JBGS and one in Neurosurgery, where
15 there is a significant reduction in deep infections
16 with putting vancomycin in the wounds. So we know
17 that vancomycin will eventually come up with VRE,
18 so there may be a place for that.

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

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

3 DR. BADEN: Ms. Hugick?

4 MS. McVEY HUGICK: Joy McVey Hugick.

5 Because FDA's data was limited and didn't include
6 specialty hospitals such as children's hospitals, I
7 was curious in your monitoring of sales data, if
8 you saw what it looked like as far as children's
9 hospitals, and/or if you know if anyone's using it
10 for its indication. I'm guessing no, but I'd love
11 to hear your insights.

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

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

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

10 (Pause.)

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

14 (Laughter.)

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

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

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

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

8 DR. BADEN: Of course.

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

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

14 DR. WONG: Okay.

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

17 DR. WONG: Okay.

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

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

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

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

5 Ms. Hugick, a follow-on?

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

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

14 MS. McVEY HUGICK: discussion.

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

22 Dr. Ofotokun?

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

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

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

21 DR. BADEN: Dr. Green?

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

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

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

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

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

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

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

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

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

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

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

9 DR. BADEN: No, no --

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

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

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

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

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

3 Dr. Swaminathan?

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

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

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

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

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

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

1 (Laughter.)

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

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

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

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

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

20 DR. BADEN: Thank you.

21 Back to clarifying questions. Dr. Burgess?

22 CAPT BURGESS: In your conclusion, you

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

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

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

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

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

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

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

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

1 clinical breakpoints for many antibiotics, which
2 are not very commonly used, particularly
3 parenterally. Nevertheless, in studies that have
4 looked at resistance patterns of microbial
5 epidemiology, particularly with respect to bacteria
6 like MRSA or C. difficile, where there's great
7 interest in evolving patterns of resistance, the
8 drug concentrations that are clinically considered
9 relevant, even though there are no official
10 clinical breakpoints, are those that would, by
11 comparison to previous
12 pharmacokinetic/pharmacodynamic data, not be
13 achievable in normal human use; for example, over
14 100 micrograms per mL of bacitracin. And there is
15 a plethora of data that demonstrates that there has
16 been very rapid evolution of resistance to
17 bacitracin with respect to multiple microorganisms
18 such as Staph aureus, Clostridium difficile
19 approaching 100 percent.

20 DR. BADEN: Dr. Farley?

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

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

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

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

1 setting?

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

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

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

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

6 DR. BADEN: Thank you. Dr. Finnegan?

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

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

20 **Open Public Hearing**

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

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. BADEN: Thank you. Will speaker number
11 2 step up to the podium and introduce yourself?
12 Please state your name and any organization you're
13 representing for the record.

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

22 I was also the US/UK global innovation

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

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

11 According to WHO this year's report listed
12 that antibiotic resistance in the non-communicable
13 diseases is the number 5 and number 2 among the top
14 10 global public health challenges. As we know,
15 non-communicable diseases right now is responsible
16 for over 70 percent of all the deaths worldwide,
17 and in recent years, gut microbiota dysbiosis is
18 recognized as an important risk factor contributing
19 to diseases such as diabetes and obesity,
20 cardiovascular diseases, cancers, C. diff
21 infection, as well as autoimmune diseases and
22 neurological disorders, et cetera.

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

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

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

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

4 With my background in the past 30 years,
5 I've invested my professional life in studying
6 horizontal gene transfer in lactic acid bacteria,
7 rapid detection of micro organisms in foods, hosts,
8 and environmental samples, and we are the group
9 that defined first honeycomb biofilm in the early
10 2000, using *Listeria monocytogenes* as the model
11 organisms.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 In addition to antibiotics, more than
2 25 percent of non-antibiotic drugs are now known to
3 impact the gut microbiota as well. So the points
4 that we discussed right here, administration as
5 well as excretion route, probably impact those
6 drugs as well. At this point, we believe that now
7 knowing the real causes to the problems, it makes
8 prompt drug treatment with minimized side effects
9 potentially an achievable goal. If we look at the
10 strains of massive antibiotic resistance versus the
11 rise of those modern diseases mentioned, they had a
12 strikingly similar strain. If the common cause is
13 oral drugs, then that makes sense.

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

1 drugs

2 The take-home message is now there are over
3 250 million antibiotic prescriptions given annually
4 in the United States alone, and mostly probably
5 given by oral, and that impacts every child and a
6 family. We're seeing a massive change of some of
7 those non-communicable diseases from rare
8 incidences now becomes an epidemic in the
9 population. There are four. There is a stressing
10 need for paradigm changes in policies and practices
11 impacting medicine, pharmacy, as well as
12 food/animal production.

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

21 Overall, we have made this discovery about
22 8 years ago, but in the past 8 years, this

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

13 DR. BADEN: Thank you.

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

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

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

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

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

12 DR. BADEN: Closer to the mic, please.

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

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

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

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

3 DR. BADEN: Dr. Swaminathan?

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

11 DR. BADEN: Thank you.

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

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

22 DR. FINNEGAN: Yes. We use spacers or we

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

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

11 DR. FINNEGAN: I have no idea.

12 DR. BADEN: Dr. Meisel?

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

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

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

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

7 DR. MEISEL: Any of the adverse event data.
8 The 12 cases from PubMed were reported, and it
9 talked about bacitracin. But the other ones on
10 slide, I guess 13, were clearly bacitracin on its
11 own. I'm just wondering if there might have been
12 more or additional cases identified in PubMed or in
13 FAERS because of a quirk in the keywords. It was
14 really a triple antibiotic irrigation with
15 3 nephrotoxins, but bacitracin wasn't one of the
16 keywords; if something may have gotten missed.

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

19 DR. BADEN: Please state your name.

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

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

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

9 In looking at it, it looks like in the early
10 '70s, concern arose, and there seemed to be a
11 shift. There have been subsequent discussions and
12 agency reviews. In the pre-digital age, the
13 records are not easily obtainable, but if what I'm
14 hearing correctly from the various agency
15 activities, from our industry colleague, and from
16 what many of us have tried to find on PubMed and
17 otherwise, I can't find any evidence of any -- I
18 will call it systemic use, but IM/IV use in the
19 last 40 years.

20 Dr. Siberry?

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

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

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

15 Dr. Green?

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

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

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

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

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

19 Dr. Burger?

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

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

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

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

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

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

17 DR. BADEN: Yes. Ms. Hugick?

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

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

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

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

1 as well as other information you may suggest.

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

7 MS. McVEY HUGICK: Thank you.

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

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

14 DR. BADEN: But it's unusual.

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

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

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

22 DR. BADEN: Dr. Stovall?

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

9 DR. BADEN: Dr. Caldwell?

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

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

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

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

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

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

4 DR. BADEN: Please?

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

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

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

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

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

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

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

1 regarding labeling.

2 DR. BADEN: Thank you. Other clarifying
3 questions?

4 (No response.)

5 **Questions to the Committee and Discussion**

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

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

1 experts --

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

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

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

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

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

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

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

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

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

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

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

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

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

17 DR. BADEN: Dr. Saine?

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

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

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

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

8 DR. SAINÉ: Yes. Thank you.

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

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

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

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

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

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

1 that's from an adult perspective.

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

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

7 Dr. Meisel?

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

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

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

18 DR. BADEN: It would be very difficult.

19 Dr. Swaminathan?

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

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

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

22 DR. BADEN: One thing I will say is we

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

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

14 DR. BADEN: Dr. Burgess?

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

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

4 DR. BADEN: Dr. Ofotokun?

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

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

1 DR. BADEN: Dr. Gripshover?

2 DR. GRIPSHOVER: [Inaudible - off mic].

3 DR. BADEN: Other discussion?

4 (No response.)

5 DR. BADEN: I guess one other discussion
6 point that's very, very challenging is not the
7 complete lack of data but near complete lack of
8 data, and that the data we're asked to evaluate are
9 50 years old, which makes it incredibly
10 challenging. The generation of contemporary data
11 is not incentivized, so the ability for us to have
12 the microdata that was alluded to before, some of
13 the PK data, or the fact that there aren't
14 breakpoint data, speaks to how the community at
15 large is not invested in understanding this, and
16 that puts us in an extremely challenging position,
17 but that is my understanding from everything
18 presented, and the agency obviously is in the exact
19 same position.

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

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

5 Dr. Weina?

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

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

10 DR. WEINA: Yes, absolutely.

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

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

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

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

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

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

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

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

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

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

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

18 (No response.)

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

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

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

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

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

11 (Voting.)

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

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

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

1 next. Shall we start with Dr. Caldwell?

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

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

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

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

21 DR. BADEN: Dr. Gripshover?

22 DR. GRIPSHOVER: Hi. Barb Gripshover. I

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

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

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

1 DR. BADEN: Dr. Weina?

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

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

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

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

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

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

1 antibiotic shortages, and might this agent have
2 some value.

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

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

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

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

12 Dr. Clark?

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

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

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

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

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

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

3 DR. BADEN: Dr. Ofotokun?

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

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

16 DR. BADEN: Dr. Burgess?

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

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

4 DR. BADEN: Dr. Swaminathan?

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

18 DR. BADEN: Ms. Krug?

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

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

8 DR. BADEN: Thank you. Ms. Hugick?

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

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

22 DR. SAINÉ: Deb Saine. I voted no. I

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

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

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

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

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

5 DR. BADEN: Dr. Stovall?

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

21 DR. BADEN: Dr. Burger?

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

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

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

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

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

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

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

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

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

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

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

17 Dr. Burger?

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

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

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

9 DR. BADEN: Dr. Meisel?

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

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

22 DR. MEISEL: I was 65 years old at that

1 time.

2 (Laughter.)

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

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

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

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

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

22 As a matter of fact, the CDC definition,

1 1992 definition of surgical site infection, has
2 never been validated. The CDC doesn't even have a
3 standard definition for pus, so we're dealing
4 with -- when all of our outcomes are based on
5 something we can't even define, it's very difficult
6 to find differences when we're looking at things
7 that are used and locations [indiscernible].

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

18 DR. BADEN: Thank you. Dr. Meisel?

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

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

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

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

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

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

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

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

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

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

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

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

15 Dr. Siberry?

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

1 their practice on many different factors.

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

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

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

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

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

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

17 DR. BADEN: Dr. Green?

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

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

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

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

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

3 DR. BADEN: Dr. Weina?

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

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

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

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

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

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

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

6 DR. BADEN: Thank you.

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

9 I do appreciate, Dr. Weina, that you
10 listened to my comments. Thank you. I think the
11 community is auto-corrected. Without using it for
12 40 years, the community has voted with their
13 practice. Though there is fear that there may be
14 wanton, unbridled use systemically, it hasn't
15 happened.

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

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

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

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

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

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

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

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

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

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

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

22 Dr. Clark?

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

3 (Laughter.)

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

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

20 DR. BADEN: Thank you. Dr. Follmann?

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

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

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

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

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

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

9 DR. BADEN: Dr. Ofotokun?

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

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

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

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

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

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

3 DR. BADEN: Thank you. Dr. Burgess?

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

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

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

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

7 DR. BADEN: Thank you. Dr. Swaminathan?

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

15 DR. BADEN: Your support is appreciated.

16 DR. SWAMINATHAN: Yes.

17 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 DR. BADEN: Thank you. Ms. Krug?

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

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

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

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

6 DR. BADEN: Thank you. Ms. Hugick?

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

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

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

6 DR. BADEN: Thank you. Dr. Saine?

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

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

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

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

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

12 DR. BADEN: Thank you. Dr. Finnegan?

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

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

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

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

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

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

4 DR. BADEN: Thank you. Dr. Stovall?

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

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

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

3 DR. BADEN: Dr. Burger?

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

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

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

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

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

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

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

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

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

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

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

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

10 DR. BADEN: Dr. Finnegan?

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

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

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

22 DR. BADEN: Yes, it affected the growth of

1 Staph aureus done at Columbia in New York.

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

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

13 DR. BADEN: Thank you.

14 Any final comments from the agency?

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

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

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

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

9 **Adjournment**

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

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

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