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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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PUBLIC WORKSHOP - ORTHOPEDIC DEVICE-RELATED INFECTIONS

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M E E T I N G

(8:00 a.m.)

DR. PEAT: Good morning and welcome to the inaugural Orthopedic Device-Related Infections Workshop. My name is Captain Raquel Peat, I am the director for the Office of Orthopedic Devices in the Office of Product Evaluation and Quality in the Center for Devices and Radiological Health at FDA. I'm excited about today's schedule of events as this is the first of a series of workshops to improve our understanding of infections related to the use of orthopedic medical devices.

This morning our opening remarks will be given by Dr. William Maisel, who is the Director for the Office of Product Evaluation and Quality and the Center medical officer at FDA's Center for Devices and Radiological Health. He is responsible for providing leadership in the development, implementation, execution, management, and direction of the Center's broad national and international postmarket, premarket, and compliance programs. Prior to joining FDA, Dr. Maisel was an associate professor of medicine at Harvard's Medical School with more than 15 years of clinical experience as a board certified cardiologist. I will now turn to Dr. Maisel to continue with the opening remarks for our workshop. Thank you, and enjoy the rest of the workshop.

DR. MAISEL: Good morning, and welcome to the inaugural Orthopedic Device-Related Infections Public Workshop. My name is William Maisel, Chief Medical Officer and Director of the Office of Product Evaluation and Quality at FDA's Center for Devices and Radiological Health.

This workshop is envisioned as the first in a series of such workshops intended to promote public understanding of the impact of infections relating to orthopedic devices, and to explore strategies and ongoing efforts to address this public health problem. While this public workshop is not intended to communicate any new policies, processes, or

interpretations regarding medical device marketing authorizations, our hope is that it will serve to facilitate further efforts, discussions, and collaborations towards the development and implementation of new innovative technologies tailored to control and mitigate orthopedic device-related infections. This effort supports CDRH's vision that patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.

Infections continue to exact tremendous costs in pain, debilitation, and mortality on the growing number of patients receiving orthopedic implants. Infection rates for hip and knee replacement recipients are usually less than 1 and 2% respectively during the first 2 years post-implant, but can increase substantially higher, 5 to 40%, if a revision becomes necessary. Approximately 5% of internal fixation devices become infected and whereas the incidence of infection after internal fixation of closed fractures is generally low, the incidence of infection after fixation of open fractures can exceed 30%.

The current economic cost of periprosthetic joint infections has been estimated to exceed $1.5 billion annually. These staggering costs to patients, both clinical and economic, mandate a high priority in the development and implementation of innovative devices and products focused on new and innovative infection control technologies. As a means of achieving this aim, this workshop is intended to provide a forum to facilitate the exchange of information among interested stakeholders, including the healthcare community, medical device manufacturers, academia, government agencies, and patients.

Today's workshop will address numerous topics intended to prompt dialogue, discussion, and collaboration. Today's presentations will include overviews of the current state of technology and treatment strategies for infection control in conjunction with orthopedic surgeries including, in particular, those for acute trauma or chronic osteomyelitis.

There will be discussions focused on identifying the most critical unmet needs and knowledge gaps impeding our ability to achieve our goal of minimizing the occurrence in mitigating the severity of orthopedic device-related infections.

We'll discuss the current and emerging technologies available to help control infections in orthopedic surgeries. Specifically, we'll cover polymethyl methacrylate bone cements and spacers, device coatings, surface modifications for arthroplasty devices, and biodegradable delivery systems for infection control products.

We'll discuss the particular hurdles, including regulatory challenges, in proceeding from the bench level to marketing and clinical implementation of new and innovative infection control devices and products.

We'll also have an opportunity to discuss how collaborative efforts among device manufacturers, the clinical community, academic institutions, patients, and government agencies can best be utilized to prioritize the rapid availability of new and innovative infection control technologies, as well as how patient preferences can best be leveraged and utilized to achieve this aim.

I wish to thank in advance all of today's moderators and speakers, and thank Dr. Parvizi, Dr. Tornetta, Captain Peat, and others in FDA who took part in planning and organizing this event. And I would especially like to thank each one of you for participating in this workshop.

Lastly, I'd like to introduce our master of ceremony for this workshop, Dr. James Bertram. Dr. Bertram joined FDA in 2009 as a regenerative medicine fellow in the Commissioner's Fellowship Program after completing his Ph.D. from Yale University. He is currently an assistant director with the Regulation, Policy, and Guidance Staff in CDRH's Office of Product Evaluation and Quality. In addition, he serves as a CDRH product jurisdiction officer collaborating across FDA in crosscutting policies, many of which apply to

the review and regulation of combination products. I'll now turn the workshop over to Dr. Bertram, and I thank you and hope you enjoy your first of many workshops of this kind.

DR. BERTRAM: Thank you, Captain Peat and Dr. Maisel, for the opening remarks and introductions. It is an honor to be here today and I hope everyone is as excited as I am to be part of this inaugural workshop.

I'm sure everyone has had an opportunity to look at the agenda, which is divided into four sessions, each culminating with a discussion panel with the presenters from the respective sessions. As you can tell, we have a very busy day with numerous diverse presentations from various stakeholders.

Just a reminder. This is intended to be a series of workshops envisioned to improve public understanding of infections related to orthopedic devices and appropriate mitigation measures for protecting and promoting public health in this clinical area. Given the breadth and complexity of the product topic, the focus of this inaugural workshop is the role specifically of medical devices in orthopedic infections.

That being said, we have a diverse lineup, a number of presentations from various stakeholders focused on products that may be regulated as drugs and/or combination products by the various Agency centers. A combination product, for those that don't know, is a product that is comprised of both a device, drug, and/or biologic.

While we look forward to hearing perspectives on such products from our various stakeholders today, as I indicated, we intend for this to be a series of workshops. Therefore, while today's meeting may be a good springboard for discussions and perspectives, more substantive engagement regarding development and associated regulatory considerations for such products will be topics for future workshops.

With that, let's get things started. I'd like to introduce Session 1, titled "Orthopedic Infections and the Role of Medical Devices in Orthopedic Infections." Our first presenter to

kick things off will be Dr. Javad Parvizi. Dr. Parvizi is a board certified orthopedic surgeon and has been at the Rothman Institute since 2003. He specializes in the management of young patients with hip disorders such as dysplasia and femoroacetabular impingement. He completed his medical school education in the United Kingdom, he has served as the president of the Musculoskeletal Infection Society in 2013, and the Eastern Orthopaedic Association in 2018. The title of his presentation: "Overview of Orthopedic Infections Involving the Appendicular Skeleton."

DR. PARVIZI: Good morning, my name is Javad Parvizi, I'm a Professor of Orthopedic Surgery at the Thomas Jefferson University. I would like to thank the FDA for providing us the podium to discuss some of the most important topics related to orthopedic infections. Next slide.

I, or my institution has received support from various organizations. Next slide.

I am also a consultant to some industry and other organizations that may have anti-infective technologies and hence, my conflict is definitely pertinent to the subject matter this morning. Next slide.

Infection is a terrible problem whenever it occurs, but infection associated with orthopedic procedures, in particular, is very challenging and very devastating, indeed. Next slide.

The reason it is very difficult to treat these infections is because infection related to orthopedic implants is usually in the form of a biofilm, a complex structure of organisms that protect themselves under an umbrella of glycocalyx, which then becomes impenetrable to antibiotics or the immune system of the host. Next slide.

And the cost associated with treating infections with implants is extremely high. Here, a table borrowed from a prior publication shows the costs associated with treating infection related to cardiovascular, orthopedic, and other surgical fields. And if you look at the

orthopedics and the huge volume of procedures that we do annually, the cost of treating these infections is immense, indeed. Next slide.

Periprosthetic joint infection is one of those challenging problems that occurs after total joint replacement. Next slide.

After primary knee replacement, infection can occur up to 3% of the time and it's the most common cause of failure of total knees. And after hips, it's the third most common cause of failure and can happen up to about 2% of the primary hip replacements. Next slide.

And when it does occur, it carries huge morbidity and mortality and is a truly devastating complication that leads to loss of a limb and sometimes loss of lives. Next slide.

In a study that we published from Rothman, we noted that the survivorship after periprosthetic joint infection is very similar to other cancers such as breast and melanoma. Next slide.

In a follow-up study that I did with Dr. Kurtz and Dr. Zimmerli, looking at the Medicare population, we have found similar sobering statistics. Next slide.

We found that the incidence of PJI had not improved over time; the mortality declined slightly perhaps, but survivorship after infection of a total knee or a total hip was very similar to breast cancer and prostate cancer. Next slide.

And it shows that the incidence and economic burden of PJI is still on the rise. Next slide.

In this projection study I did with Dr. Kurtz, we noted that the incidence of infection was un-exponential rise. Although this was met with some skepticism initially, the follow-up studies we've done shows that we may have underestimated the economic burden and the incidence of this devastating complication. And it is possible that 60,000 of the revisions being done this year in the United States alone may be related to periprosthetic joint infection. Next slide.

At a cost of almost $2 billion. Next slide.

Periprosthetic joint infection after shoulder or elbow replacement is also not uncommon. Next slide.

It can happen up to 4% of the time after primary shoulder arthroplasty and is the most common cause of revision. Next slide.

In this great study done by Dr. Namdari from my institution, we see that the number of shoulder arthroplasties being done annually continues to increase and the associated infection is also on the rise. Next slide.

The treatment of infection after shoulder arthroplasty is also very difficult, both in terms of clinical as well as having economic impact on the society. These patients require prolonged courses of treatment and multiple surgical interventions most of the time. Next slide.

The subject of infection after trauma will be covered by my trauma colleagues, particularly Dr. Tornetta will be giving some talk of this. Next slide.

I will not dwell on this too much, but we know that infection after fixation of fractures can happen either early or delayed fashion or late and the late infections can be related to chronic osteomyelitis and infected nonunions, which are, of course, extremely challenging to treat. Next slide.

And these are usually associated with multiple reoperations, long courses of antibiotic treatment, delayed healing, permanent functional loss and sometimes the loss of a limb. Next slide.

Its incidence varies depending on the energy of the fracture. Low energies may be lower incidence of around 1 to 2%, but with high energy and common mutant, particularly open fractures, the incidence can be up to 30%. And unfortunately, when infection after fracture fixation occurs, the success rate is not perfect and recurrence of infection or complication can happen up to 30% of the time. Next slide.

The cost associated with treating infection after fracture fixation when infection

happens is twice that of without the infection. Again, huge economic burden. Next slide.

Spine is another field which is very challenging. Next slide.

If an infection after spine surgery has occurred, it can lead to devastating complications such as neurologic compromise, sepsis, and death. Next slide.

Infection can happen up to 16% of the time and it does depend on the type of surgery, the length of the surgery, the approach, etc., but it is not an uncommon complication. Next slide.

It increases the morbidity to patients, results in pseudarthrosis, and almost half of these leads to chronic wound issues, neurologic compromise, systemic sepsis, and even death. And of course, it has huge economic burden on healthcare as some of these can cost up to $200,000 to treat. Next slide.

So this was a very quick overarching presentation related to economic as well as the clinical burden of treating implant-related infections. I hope this has been of some interest to you. Thank you very much.

DR. BERTRAM: Thank you, Dr. Parvizi.

Our next speaker is Dr. John Segreti. He graduated summa cum laude from Loyola University of Chicago with a B.S. in biology in 1976. He received his medical degree from Rush Medical College in 1980. Dr. Segreti completed his residency in internal medicine in 1983 and a fellowship in infectious diseases in 1986, both at Rush Presbyterian-St. Luke's Medical Center. He is board certified in internal medicine and infectious diseases, and is currently a professor in the Department of Internal Medicine, Division of Infectious Diseases at Rush Medical College. He is also hospital epidemiologist and chair of the Infection Prevention and Control Committee at Rush University Medical Center. The title of his presentation: "Orthopedic Infections - Current Medical Treatment Recommendations and Associated Concerns."

DR. SEGRETI: Hello, my name is John Segreti and I will talk today about antibiotic treatment of orthopedic infections, current recommendations, and the problem of antimicrobial resistance. I have no financial relationships to disclose.

And in general, when it comes to infections associated with surgical implants, infection is not very common. However, a very low inoculum is often enough to cause infection and low virulence organisms are more likely to be seen as pathogens. Mortality is generally very low, but morbidity and cost can be very high.

In terms of how the foreign bodies get infected, typically it's by either direct inoculation at the time of surgery, direct extension from infected soft tissue, or hematogenous seeding. One of the issues associated with foreign body infections and one of the difficulties in being able to eliminate foreign body infections is that most bacteria, when they attach to a foreign body, can form a biofilm.

Biofilms are complex communities of microorganisms embedded in an extracellular matrix that forms on surfaces. It can be monomicrobial or polymicrobial and they can survive for a long time and consist of subpopulations of organisms that can either be the same genetic characteristics or can have different genetic characteristics.

The reason biofilms are important is that they often persist despite aggressive antimicrobial therapy and intact immunity. Treatment usually requires removal of the object on which the biofilm has formed, in addition to antimicrobial therapy.

In terms of the microbiology of orthopedic infections, gram-positive bacteria such as *Staphylococcus aureus* and coagulase-negative *Staphylococci* are the most common followed by *Streptococci*. Gram-negatives such *Pseudomonas*, *E-coli*, *Klebsiella*, are seen in about 15 to 20% of cases and about 15% of cases are culture-negative.

In terms of antibiotic resistance, the good news is that we're seeing less MRSA. However, we are seeing more *Klebsiella* and *E-coli* resistance to third generation cephalosporin,

so-called extended spectrum beta-lactamase producing gram-negatives. And there is an increase in carbapenem-resistant *Klebsiella* and *E-coli*, although again, fairly low percentages in certain locations can be much more common and associated even with foreign body infections.

Treatment of infected prostheses and other foreign bodies typically involves surgical removal of the device, especially if loose or nonfunctional; culture-directed systemic antibiotics, although salvage may be successful in early infection and there's still a question about the role of chronic suppression in some patients.

The recommended therapy for infected prostheses depends on whether it is an early or late infection and there are a variety of different definitions for what's early and late. The one that's most commonly used is that early postoperative infections are within 1 to 3 months of surgery, and 6 weeks of systemic antibiotics may be tried and we recommend retaining the prosthesis if it's not loose. Late chronic infections typically require removal of all the components as antibodies alone may not be successful in clearing the infection.

Acute hematogenous infection can occur either early or late and typically, the time period is the same as early post-op and that if there are signs and symptoms for less than a few weeks, you may be able to treat with retention of the prosthesis; however, if the prosthesis is loose, it will require removal.

Management of these complex orthopedic infections usually includes a prolonged course of intravenous antibiotics. However, in this study from *New England Journal of Medicine*, patients from a variety -- from 26 surgical centers in the UK were enrolled and were treated with either IV or oral antibiotics and this was a prospective randomized trial.

What is shown here is that oral antibiotic therapy was non-inferior to intravenous antibiotics when used during the first 6 weeks for complex orthopedic infections and the endpoint was a treatment failure at 1 year.

Rifampin is often used by people in addition to primary antibiotics for treatment of

orthopedic infections because of its ability to kill bacteria in biofilm. And in this particular study, while rifampin was not randomized, investigators could decide to add rifampin if they wanted to and no rifampin was used in about 60% of the people randomized to IV antibiotics, and no rifampin was used in 44% of people randomized to oral antibiotics. And there were a variety of total length of therapies of rifampin usually from about 2 to 6 weeks, although in 20 to 30% it was used for more than 6 weeks. And based on this study, there was no difference in the people that received rifampin versus people who did not receive rifampin in terms of failure at 1 year.

This is another study that took a look at 5-year survival of periprosthetic joint infections due to gram-positive organisms according to treatment type, and they compared monotherapy with rifampin versus monotherapy without rifampin and they found that the type of antibiotic that was used affected outcomes. For example, if rifampin was added to levofloxacin, ciprofloxacin, or amoxicillin, there was no difference between monotherapy without rifampin or a combination therapy with rifampin. However, if rifampin was added to linezolid, trimethaprim/sulfa, or clindamycin, people actually had a worse outcome and it turned out that rifampin decreased the serum levels of linezolid, trimethaprim/sulfa, and clindamycin.

So this is a more recent study looking at rifampin combination therapy in *Staphylococcal* periprosthetic joint infections. It was a prospective randomized trial, unfortunately not a very large trial, but there was no statistical difference between people who got rifampin combination versus monotherapy.

Finally, this is a study that was recently published that looked at patients who were undergoing two-stage revision for knee or hip infections and this was a multicenter, randomized controlled trial that showed that 3-month course of microorganism-directed oral therapy significantly reduced the rate of failure due to further infection following a two-stage revision of hip or knee arthroplasty for chronic periprosthetic joint infection.

So in conclusion, joint arthroplasties are life-enhancing for millions of people around the world.

Large, high-quality, multi-institutional studies are necessary to more accurately identify optimal approaches to treatment.

And because of high morbidity and cost associated with periprosthetic joint infections, better preventive strategies are needed to impact the anticipated increased number of PJI cases in the future. Thank you.

DR. BERTRAM: Thank you, Dr. Segreti.

Next up is Dr. Bryan Springer. Dr. Springer completed his residency in orthopedic surgery at the Mayo Clinic with fellowship in adult reconstruction of the hip and knee at the Harvard School of Medicine/Brigham and Women's Hospital. He's currently an attending orthopedic surgeon at the OrthoCarolina Hip and Knee Center in Charlotte, North Carolina, where he serves as a fellowship director and is Professor of Orthopedic Surgery at the Atrium Musculoskeletal Institute. He is the co-founder and medical director of Operation Walk Carolinas. He has published over 120 scientific articles in peer-review literature and authored over 25 book chapters. The title of his presentation: "Systemic and Local Toxicity Associated with Delivery Technologies."

DR. SPRINGER: It is my privilege to present to you today systemic and local toxicity of antimicrobial delivery technology.

These are my disclosures relevant to this talk.

I've really been interested in this topic of systemic safety of antibiotic delivery systems since I was a resident, and we initially published this article in 2004, looking at the systemic safety of very high doses of antibiotic-loaded cement following resection of total hip and knee arthroplasty.

So what are the goals of antibiotic delivery, specifically with regards to periprosthetic

joint infection? It's good we understand it's balancing the optimal efficacy of the antibiotic versus the safety profile, being able to deliver effective concentrations to the site of infection while also minimizing systemic toxicity associated with that delivery.

The problem that we face in periprosthetic joint infection and many other device-related infections is the issue of biofilm. Of course, as we know, and as we'll hear later today in subsequent talks, the majority of our infections that occur in periprosthetic joint infection, such as those with *Staph aureus*, *Strep*, and *Pseudomonas*, have a very high affinity to form biofilm and the majority of our infections are not bacteria floating around as planktonic bacteria, but more in the formation of this community of bacteria which we call a biofilm.

I think it's important to understand when we talk about antibiotic concentrations, oftentimes and in many laboratories, we're reporting the minimal inhibitory concentration, which is the concentration that's required to inhibit bacterial growth. However, when we are specifically talking about infections that occur in a biofilm form, it is more appropriate to use the minimum biofilm eradication concentration, and this is the lowest concentration that's capable of killing these bacteria that have formed biofilms. The challenge, of course, is that this is often 100 to 1,000 times higher than what's reported as the minimal inhibitory concentration.

And so oftentimes in periprosthetic joint infection, we're left with clinical pictures that look like this. This unfortunate gentleman has been through six surgeries. He's been on six or eight different courses of IV antibiotics, he has persistence of infection despite systemic and the local antibiotic delivery, and now is facing issues with significant soft tissue coverage due to his multiple surgical debridements and treatment with antibiotics.

I think the question we always have to ask ourselves with regards and specific to periprosthetic joint infection is, is our entreatment improving over time? And this was a somewhat sobering article that was published in the *Journal of Arthroplasty* recently that

looked at our success rate in treating periprosthetic joint infection from 2000 to 2010 and then over the subsequent 5 to 6 years, and you can see there's really been no change in the success rate between the two groups of cohorts compared together and that, in fact, our overall success rate for the treatment of periprosthetic joint infection has not significantly improved. Along those same lines is when we compare aseptic revisions with septic revisions.

We can see dramatic differences in morbidity and mortality with those patients that have deep periprosthetic joint infection. And if you want to put that into relative terms, I think it's important to look at that mortality compared to many of the common types of cancer in the United States, and you can see the 5-year mortality for periprosthetic joint infection is 25% higher than several of the most common cancers that we treat in the United States.

So we face significant challenges not only in treating these patients' infections, but also dealing with some of the systemic ramifications of their treatment, as well. So here's really our challenge, how do we deliver these doses of antibiotics at high concentrations that really reach that minimum biofilm eradication concentration, as it's not related to the minimal inhibitory concentration to deliver those concentrations locally and systemically without creating systemic toxicity, and ultimately end up with a successful treatment of periprosthetic joint infection?

I think one of the questions we have to ask ourselves is what is really the role of systemic antibiotics, and I think we all know it's the delivery of effective concentrations to the site of infection. In my mind, this really is adjuvant treatment to the local delivery of antibiotics and sustained delivery of antibiotics to the site after the local delivery has tapered off. But we also have to realize that that systemic delivery protects our host from sepsis, and also many of our patients that we treat with periprosthetic joint infection also have other joint replacements in place that are at risk for spread or development of periprosthetic joint infection.

So what really is the ideal systemic antibiotic agent? Ideally, we'd want it to be cost

effective, regularly available for our patients in dosing concentrations that is manageable, that we're able to obtain sufficient concentrations at the site of infection; in our case, the site of bone, soft tissue, in periprosthetic joint infection. Ideally, we'd want it to be bactericidal and as we've mentioned, have good activity in penetrating biofilm for treatment.

The challenge, of course, and this is just one example of several of the antibiotics that we typically use, is that when you look at the percent of serum-to-bone concentration, it's relatively low. For most of our commonly used antibiotics, the amount of antibiotic that gets to the bone can be relatively low, somewhere in the order of 5 to 20% for the most common types of antibiotics that we use, typically both oral and intravenously.

And the overwhelming majority of these antibiotics at the concentration that's delivered to the site have very poor biofilm activity and also associated with significant adverse effects to the host, ototoxicity, nephratoxicity, some cardiac issues.

And so again, we're back to this issue of the benefits of the antibiotic versus the toxicity and we know that systemic antibiotics, it's not just about delivering a dose, it's about delivering that dose over a prolonged period of time for that antibiotic to be effective. In fact, a current standard of practice from the Infectious Diseases Society requires long treatment durations and generally, in most of our patients, that's a minimum of 6 weeks of intravenous antibiotic therapy.

And now I think it's worth mentioning that we're seeing, in the treatment of many of these patients with periprosthetic joint infection, a significant trend for chronic suppression, not only for high-risk patients, but for all of our patients undergoing periprosthetic joint infection, a trend for prolonged or even life-long chronic suppression with oral antibiotics to try and reduce their risk of recurrence and of course, that long-term use of oral antibiotics can also be associated with long-term toxicity, as well, that needs to be taken into consideration.

And so we see in the literature several reports from the general medical population of

nephratoxicity associated with many of our commonly used antibiotics such as vancomycin, and oftentimes we are combining many of these agents for dual therapy and the general medical population would suggest that up to 40% of patients in the general medical population can have nephratoxicity with the use of antibiotics. And we can see in this table on the right some of the potential risk factors and when we look at this in context of the patients that we're treating with periprosthetic joint infection, they really meet the majority of the risk factors.

The total daily dose is high, the duration is long, many of our patients are obese, they have underlying comorbidities, they're getting concurrent nephrotoxin exposure from local delivery and oftentimes again, as we mentioned, we have dual antibiotic therapy that increases their risk for getting systemic toxicity. And this has also been shown in the periprosthetic joint infection literature where the relative rates of acute kidney injury after treatment for periprosthetic joint infection can be in the range somewhere of 20 to 35%.

Let's talk for a minute about local antibiotics and elution characteristics, and this is going to be touched on in much more detail in some of the subsequent talks. The challenge we face, of course, with our local antibiotic deliveries is that it's highly variable. This is just a video of me mixing antibiotics into cement.

It depends on the type of cement, the dosage that's being used, how it's mixed, the surface area that's available for that elution. And most antibiotic spacers, if you look at studies, both basic science studies and clinical studies suggest that only about 15% of that antibiotic is actually eluted from the spacer, that in fact, those peak elution times occur over the first 48 to 72 hours and typically, by Day 5 the elution characteristics from that antibiotic cement spacer reach sub-therapeutic levels which, of course, then placed that patient at risk for colonization and reinfection.

And although the overwhelming majority of studies have shown systemic safety of local antibiotic delivery, again, these patients are oftentimes ill, they're oftentimes receiving

concomitant systemic therapy, and so there have been case reports in the literature about acute renal failure associated with that variability in high-dose, local concentration delivery, systemic absorption over a short period of time relating to issues with diminished renal function.

Fortunately, when we look at some of the basic science studies that show this is local delivery of these high doses a concern for muscle tissue, for bone tissues, that the doses, in particular vancomycin and tobramycin, which are most commonly used in the spacer, require concentrations that are exceedingly high to reach cell death. So most of the basic science studies and certainly, from a clinical perspective, we don't see a lot of issues of local toxicity to cells and tissue, it's more the systemic issues that we are worried about.

So in conclusion, systemic antibiotics are incapable of achieving minimum biofilm eradication concentrations at the site of periprosthetic joint infection without systemic toxicity. And the risk of overall systemic toxicity remains high for multiple reasons that I outlined.

The current local delivery of antibiotic-loaded bone cement has a short elution profile and high variability, and there have been case reports of systemic toxicity related to that variability.

What we need to do, however, is continue to innovate safe and effective antimicrobial delivery mechanisms to help our patients with periprosthetic joint infection to achieve high concentrations locally at the site with minimal systemic toxicity.

And I'll just leave you with a quick thought from a recent article that we published looking at adjuvant antibiotic-loaded bone cement, concerns with current use, and research to make it work. And I highlighted just one area of this article where it states, "The profitability of seeking FDA approval for antibiotic combination devices limits the incentive for industry to pursue innovative antibiotic delivery systems, "which, again, I think are critically necessary.

"However, innovative regulatory pathways, similar to the limited population

antibacterial drug approval mechanisms may be a valuable pathway to seek approval for the use of new antibiotic loaded devices in a smaller, more targeted patient population with high risk of infection." Thank you very much for your attention.

DR. BERTRAM: Dr. Springer, thank you.

With that, I would like to introduce Dr. Yale Fillingham. Dr. Fillingham graduated from Dartmouth College with a major in biophysical chemistry and received his medical degree from Rush Medical College. After completing a residency in orthopedic surgery at Rush University Medical Center, he completed a fellowship in adult reconstruction surgery at the Rothman Institute. He had been in practice at Dartmouth-Hitchcock Medical Center until recently returning to the Rothman Institute. He has focused his research on periprosthetic joint infection, blood management, and the development of evidence-based protocols to work towards standardization of patient care. The title of Dr. Fillingham's presentation: "Current State of Periprosthetic Joint Infections of the Hip and Knee Arthroplasties."

DR. FILLINGHAM: Good morning. I'd like to start by thanking the FDA for organizing the workshop on orthopedic infections. It goes without saying, periprosthetic joint infection is the complication that haunts any arthroplasty surgeon. We will start by covering definitions that are important when deciding on a treatment, followed by a review of common treatments.

The following are my disclosures, none of which are relevant to my presentation.

Before we can discuss treatment options, we need to know the definition of PJI. Not always is the diagnosis as blatant as it was for this patient. For a while, we simply defined PJI similar to Justice Stewart's definition of obscenity as "I know when I see it." As you can imagine, this definition leads to a lot of inaccuracies.

After observing the difficulty of treating patients and researching PJI without a standard definition of PJI, Dr. Parvizi and MSIS in 2011 came up with what has been termed the MSIS definition of PJI and it became the gold standard definition. It had major and

minor criteria and based on the number present, would determine if a patient was positive for PJI.

When the first definition of PJI was developed, it was largely based on expert opinions and the minor criteria underwent some refinement. Although the 2011 definition of PJI was a huge step forward, there's no way it could have been expected to be a static document. For instance, we've seen the development of new diagnostic tests and learned that not all tests are created equal in terms of diagnostic accuracy. Plus, the 2011 definition was a combination of preoperative and intraoperative diagnostics all in one. Therefore, the 2018 definition was developed to address shortcomings of the 2011 definition, and I'm sure this is not going to be our last iteration.

When it comes to the treatment of PJI, the three primary options are debridement, antibiotics, and implant retention, which is referred to as DAIR, a single-stage exchange or a two-stage exchange. Other less utilized options that we typically think of as salvage options will be antibiotic therapy alone, resection arthroplasty, fusion, or amputation. For the purposes of today's presentation, we will only discuss the primary treatment options.

Once we've made the diagnosis of PJI, timing is one of the biggest factors in the choice of treatment. For the most part, treatment options come down to retention of the implants or explant with reimplantation. Because the success of treatment with implant retention is worse when the patient is more than 3 to 4 weeks from the index procedure or symptomatic for more than 3 to 4 weeks, traditional teaching has categorized PJI as acute, acute hematogenous, and chronic, whereby acute and acute hematogenous infections got DAIR and chronic infections got either a single- or two-stage exchange.

The demarcation between acute and chronic is based on the notion that once biofilm has matured, it is difficult to achieve infection eradication, but we really don't know when biofilm matures in vivo. Then there was the category of acute hematogenous that includes

patients with a longstanding infection pre-prosthesis, who developed acute symptoms and then the infection was thought to have come from another site.

Although we use the terminology, we have gotten away from using these definitions as hard cutoffs in driving treatment decisions. Today we view it as a continuum of factors that drive our decision. Among the factors, biofilm maturity is essentially a proxy for duration of symptoms. Then, if a patient has only 2 days of symptoms, if the implants aren't stable, the patient can't be expected to have a good outcome with retention of the implants. Then you must consider the infecting organism. Is it one of the organisms that are associated with high rates of failure? Or is it an organism with sensitivities to an oral antibiotic for chronic suppression? And lastly, we must consider the health of the host.

The picture here is the flow diagram of the Infectious Diseases Society of America's clinical practice guideline that highlights the indication for DAIR. When patients undergo DAIR, the reported rates of success are broad, but today we expect it to be around 50 to 70%. We've also found patients with certain characteristics have a higher rate of success, which might help in driving your treatment decision. The reason we try to identify the appropriate patient for DAIR is because a subsequent treatment of a failure is a two-stage exchange and failure of a DAIR is associated with higher rates of failure of the subsequent two-stage exchange.

Although single-stage exchange has been described for acute infections in cementless hip replacements, the true single-stage exchange is a treatment for chronic PJI. It is much more common in Europe, but has been gaining interest in the U.S. It consists of explant and reimplantation in the same surgery followed by antibiotic therapy. The individuals who described this procedure break the operation down into four stages of preparation, initial debridement, time out, and prosthesis implantation. But don't be fooled by the simplicity of the four stages because it is a much more intricate dance. Lastly, you

must realize the procedure is not recommended for all chronic PJI patients, as the patient must meet certain criteria.

Two-stage exchange is considered the gold standard treatment for chronic PJI in the U.S., which consists of two operations. The first includes removal of the implants, debridement, and placement of an antibiotic cement spacer. Then the patient undergoes 6 weeks of IV antibiotics followed by an antibiotic holiday. The antibiotic holiday before spacer aspiration is variable, but most of us will wait at least 2 weeks. Then reimplantation is typically no sooner than 2 to 3 weeks after the aspiration, with most of us waiting longer. So you can begin to see the allure of a single-stage exchange for patients since we're talking about close to a minimum of 3 months on the early side between diagnosis and completion of reimplantation.

Several controversies exist regarding two-stage exchange, but some of the most commonly discussed are non-articulating versus articulating spacers, what antibiotics and how much to include in the spacer, and timing to reimplantation.

An RCT comparing articulating and static knee spacers found patients had better post-reimplantation range of motion and functional scores with articulating spacers, and there does not appear to be any proven difference in the rates of infection eradication between the two. However, articulating spacers aren't perfect, they can dislocate or the cement can fracture.

As for antibiotics in the cement, we have no accepted standard mixture, but my mixture is 3 g of vancomycin and 3.6 g of tobramycin per 40 g bag of cement and I'll add antifungals as necessary and make other adjustments based on any culture and sensitivity data.

Lastly, timing to reimplantation has no consensus. The historical dogma was longer was better, but some literature has shown no improvement with longer durations.

There really is no free lunch when it comes to choosing between single- or two-stage exchange. Single-stage exchange has improved quality of life-years, better patient-reported outcomes, lower cost, and decreased morbidity and mortality compared to two-stage exchange. Some have even suggested a potential for better infection eradication with single-stage exchange but you have to remember, single-stage exchange is not an operation for all comers, so it's not always an apples-to-apples comparison.

Another obstacle to broader U.S. adoption is the classic recommendation to use all cemented implants when most of us in the U.S. use cementless revision hip implants. Then, as seen here in the figure from Dr. George and Haddad's article on single-stage exchange, it can require an aggressive debridement leaving behind no collateral ligaments in the knee, necessitating a highly constrained prosthesis. And we all know constraints in arthroplasty decreases implant longevity.

Lastly, another big obstacle to adoption of single-stage exchange is the decreased physician reimbursement compared to the length of the operation.

In summary, the definition of PJI is controversial because we have yet to have a 100% sensitive and specific diagnostic tool, but the most recent iteration is the 2018 definition.

Determining the appropriate treatment option is based on a continuum of factors related to the disease and host, which is a migration from the traditional teaching that it was based on time from the index procedure or duration of symptoms.

Between single- and two-stage exchange options, two-stage exchange still remains the gold standard in the U.S. Although single-stage exchange has many potential advantages, it has several headwinds to broader adoption. But that being said, I would be surprised if I don't see it become more mainstream during my career. At the end of the day, when comparing single and two-stage, I don't think about it as an either/or kind of

operation, I think about it as they complement one another and that patients who qualify for a single-stage exchange probably should be getting a single-stage exchange and those who don't are better suited with the two-stage.

Thank you.

DR. BERTRAM: Thank you, Dr. Fillingham.

Our next speaker is Dr. Peter Giannoudis. Dr. Giannoudis has obtained his medical degree in medicine from the University of Leeds. He is a professor and chairman of the Academic Department of Trauma in Orthopaedic Surgery at the University of Leeds in Leeds, United Kingdom. The title of our next presentation: "Current State of Infections Related to Orthopedic Trauma Surgery."

Just a heads up, any viewers with a weak stomach, there are some surgery videos that are a bit graphic.

DR. GIANNOUDIS: I would like to express my appreciation to the FDA for the invitation to contribute to this workshop focusing on orthopedic device-related infections. I am Peter Giannoudis and I work in Leeds, England.

These are my disclosures.

The prevalence of orthopedic surgery trauma-related infections has been reported to range between 1 to 3%. This complication has an impact on the length of hospital stay, the patient's health-related quality of life, and an impact on the healthcare-related costs.

To simplify matters, infections may be divided into three broad categories: soft tissue related, infections of joints, and surgical site infections.

The first category of soft tissue infections, also known as celluitis, has an incidence of 650,000 admissions per year in the USA, costing in the healthcare system $3.7 billion. Clinical signs include demarcated expanding edema, swelling, warmth and tenderness around the affected area. The treatment of this type of infection consists of a course of antibiotic regime.

Infection of joints can lead to complete destruction of the joint and are also known as septic arthritis with an incidence of 29 per 100,000 patients per year. Treatment here consists of washing out the joint and just prescribing pathogen-specific antibiotics.

The third category, surgical site infections, refers to infections involving the incision or organ or space occurring after surgery. These infections lead to increased morbidity, length of hospital stay, and healthcare costs. In the discipline of orthopedic trauma, we can refer to these infections as fracture-related infections.

Consequently, these fracture-related infections have an incidence of 1% in simple uncomplicated injuries, but in high-energy open fractures of the lower extremity their incidence may rise up to 30%. The associated cost of treating those is almost doubled compared to uninfected patients.

Fracture-related infections can be subdivided into those in which the fracture has not gone into union versus those in which the fracture has gone into union. Overall, four subgroups of infections may be recognized here, including abscess formation, implant-related sepsis, intramedullary sepsis, and osteomyelitis.

The treatment of abscess formation in both patients with united and/or non-united fractures includes incision, drainage of the pus, washout and further rounds of washout as indicated, administration of antibiotics, and delayed wound closure when the infection has settled. The video shown here demonstrates the development of an abscess 3 weeks after fixation of a femoral fracture.

This is an example of implant-related sepsis in a patient whose tibial fracture healed; however, due to infection, the nail migrated through the wound of the knee joint. Treatment of this type of infection includes removal of the implant, debridement in the intramedullary cavity, reaming, as washout of the intramedullary cavity, further debridement of the intramedullary cavity using a brush, as shown in the videos. The resulting dead space can be

treated by inserting a cement rod as indicated, and finally, antibiotics are administered for a minimum period of 6 weeks.

Intramedullary sepsis is another kind of infection that can occur after the fracture has united, as shown in the plain X-ray film as well as the MRI scan in this case. Treatment of this complication includes debridement of the medullary cavity with the reamer-irrigator-aspirator device and the subsequent insertion of a cement rod for the management of dead space, as shown in the videos, as well as administration of pathogen-specific antibiotics.

Here is an example of the fourth type of fracture-related infection called osteomyelitis. This 55-year-old male had a broken heel bone that was fixed with plates and screws 4 years previously. The break united. However, he developed an infection and had two previous debridements and underwent removal of his metalwork. Despite union of the fracture, the infection persisted inside the bone and this is what we call osteomyelitis. He presented with a discharging sinus, as we see in the picture with the red arrow.

Treatment of this type of infection includes soft tissue and bone debridement and soft tissue reconstruction in the form of a muscle flap, latissimus dorsi flap in this case, and administration of antibiotics for a period of 6 weeks.

In non-united fractures, the so-called fracture nonunions, four types of infection can also be considered. In regards to abscess formation, implant-related sepsis or intramedullary sepsis, similar principles of management must be applied as previously demonstrated when the fracture is united. However, after the infection has been successfully eradicated, the underlying nonunion must be addressed. The management of the fourth category, osteomyelitis, will be illustrated in the following case.

This is a 48-year-old male 12 weeks after stabilization of his tibia with an intramedullary nail. He presented with discharging sinus and a broken tibial nail as shown in the clinical pictures and radiographs respectively.

He underwent debridement of the sinus and of the dead bone and removal of the broken implant. At the end of the debridement, he was left with a bone defect as shown in the red arrow.

The bone defect was managed with a cement spacer and the tibial nonunion was stabilized with an external fixator. He was administered pathogen-specific antibiotics for a period of 6 weeks. Six weeks later, the external fixator was removed and the induced membrane was incised, the cement spacer was removed and the bone defect was grafted with an autologous bone graft as seen in the clinical picture.

The nonunion was stabilized with a plate and the wound was closed. Four months later, he was united, as shown in the plain X-rays as well as in the CT scan. With this method of treatment, we achieved eradication of the infection and successful union of the tibia.

The principles of management of infection associated with non-united fractures could be broadly divided into algorithms.

The first algorithm can be applied when the bone remains viable and the underlying fracture fixation is stable. In this situation, we debride any necrotic tissue and we leave the hardware in place until the fracture heals. We administer antibiotics to suppress the infection for a minimum period of 6 weeks and when the fracture heals, we remove the hardware and debride the bone, as indicated.

In the second algorithm, it is clear that the bone is not viable. It is dead and must be removed. In this case, one can consider either the application of the Masquelet technique or bone transport. The objective is to convert a septic nonunion to an aseptic one. When this is achieved, bone regeneration techniques must be applied to treat the bone loss and to promote union and to restore function.

To conclude, infections related to orthopedic trauma surgery could be divided into soft tissue-related, joint-related, and fracture-related infections. Each infection has different

characteristics, clinical signs, and diagnostic features. The principles of management should be followed closely for a successful outcome as demonstrated in some of the case examples shown. Thank you very much for listening.

DR. BERTRAM: Thank you, Dr. Giannoudis. And thank you, again, to all of our presenters from Session 1.

Now it's time for our presenter discussion. Just a reminder to our viewers, please feel free to submit any questions for the presenters via the e-mail provided. This is OHT6-FEEDBACK@fda.hhs.gov.

Our moderators for Session 1 are Dr. Vincent Devlin and Dr. Richard Iorio.

Dr. Devlin obtained his undergraduate degree in premedical studies from Columbia University and doctor of medicine degree from State University of New York Downstate Medical Center. He currently serves as chief medical officer in the Office of Health Technology 6, Office of Orthopedic Devices in FDA's Center for Devices and Radiological Health. Dr. Devlin worked in clinical practice and focused on the diagnosis and treatment of pediatric and adult disorders involving the cervical, thoracic, and lumbar spine until he joined FDA in 2010.

Dr. Iorio is the chief of the Adult Reconstruction and Total Joint Arthroplasty Service and the vice chairman of clinical effectiveness at Brigham and Women's Hospital. He is the Richard D. Scott Distinguished Chair in Orthopaedic Surgery. He co-founded Labrador Healthcare Consulting Services, Responsive Risk Solutions, and the Value Based Healthcare Consortium in 2015. Dr. Iorio is a national expert in hip and knee replacement, patient optimization in the treatment of osteonecrosis, physician in hospital quality and safety, and a leader in implementation of alternate payment paradigms and quality and safety initiatives in orthopedic surgery. He's the president elect for the American Association of Hip and Knee Surgeons. With that, I'll turn it over to our moderators.

DR. DEVLIN: Good morning. We would like to start this panel discussion with a question for each of our presenters. Then we'd like to hear questions from you, our audience.

So the first question is directed to Dr. Parvizi. You have outlined how orthopedic infections remain a common and pervasive problem across orthopedic surgery, especially when implanted medical devices are present. In your opinion, what are the major factors which have limited progress in advancing the care of patients with orthopedic device-related infections?

DR. PARVIZI: Thank you very much, Dr. Devlin and Dr. Iorio. Again, thanks to the Agency for providing this very important half-a-day podium for discussion of important issues.

So unfortunately, in the field of orthopedic infections, we haven't made as much progress and our innovations have been stifled for a large part because of the following factors.

One is that the incidence of this event, as disastrous as it is, it's still very small and it prevents the conduct of clinical trials or other types of research activity that could prove the efficacy of innovations and because of that, industry and academic centers alike have refrained from engaging in some of these important clinical trials that would be able to advance our advance of science.

The second is that not much attention was paid to orthopedic infections for a long, long time and only addressing some of the major issues, other major issues in orthopedics, such as wear, osteolysis, etc., and with the rise in the incidence of infection, more and more of investigators and young minds are dedicating time to investigate this. And we have seen quite a bit of advances in the last decade or so as young surgeons are flooding towards the field to study it.

And then the third is the fact that there is such a heterogeneity in terms of the type of infections we see with the implants. As shoulder and elbow have a very different pathoetiology to foot and ankle, trauma is very different to spine, yet they all share the same type of mechanism which could hopefully lend support to try and do some of these trials in the future.

And finally, I think there's been lack of funding, a lot; for the most part, the large funding bodies have not seen this as an important issue in orthopedics and it's been very difficult to attract funding towards these type of research activities.

So these are some of the highlights and some of the problems that we face at the moment.

DR. DEVLIN: Thank you very much, Dr. Parvizi. The next question will be from Dr. Iorio.

DR. IORIO: Good morning.

Dr. Segreti, you've provided an excellent overview of the medical options for treating orthopedic infections. It would be appreciated if you could briefly comment on the role of prevention strategies including patient selection, patient optimization, MRSA screening, and infection prevention protocols like intraroom antibiotics and dilute povidone washes and other dilutional irrigants for preventing infection in operative patients.

DR. SEGRETI: Okay, thank you. I'll try to get to all of those. I think patient selection and patient optimization is crucial, so that they're choosing patients to undergo surgery with the best chance of having a good outcome and the lowest chance of having a consequence of infection.

And when you take a look at the risk factors typically associated with high risk of infection, the biggest ones are obesity, diabetes, smoking, and malnutrition, and some of these can be adjusted and some of these can be optimized prior to surgery. Obesity is

probably the hardest one to try to reverse prior to surgery, but it's worth trying. Diabetes, you want to make sure that you're screening people for diabetes, probably with hemoglobin A1c to make sure that they're not an unidentified diabetic prior to surgery and try to optimize their diabetes therapy with their internist or endocrinologist. And it's also become clear that you want to control their perioperative glucose, as well, and you want to make sure that their perioperative glucose in the 2 to 3 days after surgery is below 200. Smoking is a huge deal, you want to make sure that people have stopped smoking and again, you want to do this in conjunction with their primary care doctor. And malnutrition, make sure that there is evidence of good nutrition as possible, looking at their albumins or preopiumins to make sure that it's optimized prior to surgery.

In terms of MRSA screening, a lot of people do it. There are lots of studies that support the use of MRSA screening and decolonization, even methicillin-susceptible *Staph aureus* screening and decolonization. The problem with all those studies, even though they're fairly large, show a significant effect, they're all flawed in that they are all retrospective and for the most part, single-center studies.

There is only one prospective randomized trial of MRSA screening by Sousa in the *Journal of Arthroplasty* in 2016 that did not show any benefit of MRSA screening. Unfortunately, that was a pretty small study. So we really --

(Audio feedback.)

DR. SEGRETI: -- we definitely need larger studies looking at the benefit of MRSA screening because if you decide to do it, it's a big commitment for you and for the patient.

In terms of intrawound antibiotics and povidone-iodine and dilutional irrigants at the time of surgery, it sort of makes some sense, but not everything in medicine that makes sense necessarily will prove to be true. We were part of a study, Dr. Della Valle was the lead, that showed that povidone-iodine at the time of surgery decreased the risk of

infection. Unfortunately, subsequent larger trials have not shown a benefit. Plus, there's potential toxicity, especially if people are using different types of local therapies that could potentially cause problems with wound healing. So again, that's another area where there's a knowledge deficit and needs more information.

DR. IORIO: Thank you.

DR. DEVLIN: Thank you, thank you.

The next question is directed to Dr. Bryan Springer. Dr. Springer, in your excellent presentation you discussed nephratoxicity and briefly mentioned ototoxicity. How would you suggest that these toxicities be assessed in clinical regulatory studies for new orthopedic devices?

Also, please comment on the relevance and appropriate methods for assessing bone toxicities and the potential impairment of fracture healing or bone in-growth when investigating innovative antibiotic delivery systems.

And lastly, if you could please comment on the intramedullary delivery of vancomycin, which has been described as the optimal way to deliver high doses to the affected area without toxicity and has been championed as a technique for both PJI treatment and prophylaxis.

(Audio feedback.)

DR. BERTRAM: Dr. Springer, I believe we're having issues hearing you.

(Audio feedback.)

DR. BERTRAM: Still not better.

(Audio feedback.)

DR. BERTRAM: Still.

DR. IORIO: Jay, do you want to take that question?

DR. PARVIZI: Sure, absolutely. I think Bryan very nicely highlighted some of the

issues that we face with regard to toxicity of antibiotics being added to cement and that certainly affects the patient's systemic function, as well as the local environment of a joint. Fortunately, when you're using a spacer there is no need for any -- of osseointegration at the time. But your question, Dr. Devlin, is pertinent because at some point that spacer has got to be taken out and a new implant has to be put in and the question is does that change the internal milieu of the joint to affect that process?

We don't really have enough data to be able to answer that question with certainty, but based on data that Bryan presented and other investigators have shown, any type of antibiotic in high enough quantity is toxic to osteoblasts and chondrocytes. And it could also potentially affect the healing of fractures, which I'm sure Dr. Tornetta and the rest of the trauma team later will touch on. I don't know if that answers the question or not and I apologize, Bryan would have been able to give a much more scholarly response to that question.

DR. IORIO: Thank you very much, Dr. Parvizi, that was great. We can move on to the next question.

DR. BERTRAM: Dr. Devlin, I'm sorry to interject, just we are up to time, so if there are any other questions, we can -- please feel free to communicate them and we'll possibly try to address in a later discussion or another mechanism. But I just wanted to thank everyone again from Session 1 and notably, the discussion now. A wonderful discussion with all the presenters. What a great start for today's workshop. Right now we have a quick 5-minute break before beginning Session 2. See you momentarily.

(Off the record at 9:16 a.m.)

(On the record at 9:21 a.m.)

DR. BERTRAM: We'll now proceed to Session 2 titled "Total Joint Arthroplasty Devices: Knowledge Gaps and Development of Device Technologies to Address Unmet

Needs Related to Orthopedic Infections."

Our first speaker, Dr. Chad Krueger, is a fellowship-trained orthopedic surgeon specializing in hip and knee replacement surgery. He served as an officer in the United States Army for 9 years while practicing orthopedic surgery. He completed his fellowship training in adult reconstruction at the Rothman Orthopaedic Institute at Thomas Jefferson University Hospital. The title of his presentation is "Safety and Effectiveness Data Related to the Use of Polymethylmethacrylate Bone Cements in Infection."

DR. KRUEGER: Good morning, my name is Chad Krueger and I am one of the adult hip and knee reconstruction surgeons here at the Rothman Institute. I look forward to speaking to you today and appreciate the opportunity from the Food and Drug Administration to do so.

I have no disclosures.

Antibiotic-laden bone cement is not a new concept. It has been around since the 1970s, and yet there are very few well-constructed studies supporting its use in the past 50 years. Still, it is widely used by surgeons throughout the world in both primary and revision settings, making the investigation into its risks and benefits of great importance.

For the purposes of this talk I want to make sure everyone has a clear understanding of the various types of cement that are used in practice. We will define high-dose antibiotic cement as that with greater than 1 g of antibiotics per 40 g of cement. Low-dose antibiotics are that with 1 g or less of antibiotics per 40 g of cement. And plain cement is that without antibiotics at all.

Any discussion of the efficacy of antibiotic-laden bone cement starts with the general idea that this type of cement is able to provide a local concentration of antibiotics that is much higher than would otherwise be obtained by providing a patient with systemic antibiotics alone. This is secondary to the fact that systemic antibiotics can only be dosed

to levels that are under those levels known to be toxic to cells and organ systems.

Whereas the delivery of local antibiotics can be dosed much higher, while in theory avoiding the systemic toxicity, and when considering the importance that high antibiotic levels play when trying to eradicate bacteria and biofilm from patients with infections, having the ability to achieve local antibiotic concentration levels that are more than 100 times higher than those provided by systemic antibiotics is certainly appealing. That said, we must first consider the safety of antibiotic-laden bone cement when considering its use.

For even though the idea of bone cements with antibiotics is to increase the local concentration, it has already been shown that 20 to 25% of all periprosthetic joint infection cases treated with antibiotic bone cement allowed the systemic levels of antibiotics to reach those high enough to cause toxicity. This toxicity is typically focused at the kidneys or the liver but can also be more widespread in nature and ultimately lead to multi-organ failure.

This is seen by the picture shown here, taken from a patient who is suffering from DRESS syndrome after the placement of an antibiotic loaded cement spacer.

In addition to the systemic toxicity, antibiotics delivered from cement can also have negative effects on local tissues. Again, this is concentration and time dependent, but when considering the variability in both concentration and the types of antibiotics used for many of these constructs, as you can see here on the table, it is safe to assume that many, if not most, provide at least some type of local toxicity when used.

The other function of cement is, of course, to provide a structural construct that will hold the implants in place. This function appears to be compromised by high doses of antibiotics, in this event at levels above 1 to 2 g per 40 g of cement. At these levels, the microscopic structure changes in the cement itself and the mechanical strength of the cement is decreased. That said, many low-dose antibiotic cement constructs or those with

1 g per 40 g of cement seem to be safe in terms of mechanical strength of the cement itself.

With some of the safety discussions out of the way, we can now focus on the ever-pressing question of well, does antibiotic-laden cement work? Or more precisely, did the benefits of using antibiotic-laden bone cement outweigh the risks? And while I'd love to be able to give a better answer on this topic, the real answer is we aren't sure.

As I mentioned earlier, there is a glaring lack of high-quality, prospective, randomized controlled trials on this topic and there is so much heterogeneity in the data behind antibiotic-laden bone cement that determining a definitive answer is just about impossible.

When looking at the use of low-dose antibiotic-laden bone cement in primary total joint arthroplasty, there is a large scale of registry studies both supporting and refuting its use. One of the challenges with this topic is that the infection rate after a primary total joint arthroplasty is so low that properly powering perspective studies is a massive undertaking. And this leaves us with the registry data and large-scale institutional data to consider. The one registry that seems to continually provide support for the use of low-dose antibiotic bone cement is that from the National Joint Registry in the United Kingdom, and you can see some of the results listed on the slides here.

However, there are also other registries that don't seem to support their findings, many meta-analyses on these topics that also don't provide much robust support for this practice. This is not to say that low-dose antibiotic bone cement is not effective, but only that interpreting registry data should be done with caution.

There are many inherent biases and methodological weaknesses of these study types, such as selection bias, that really can't be controlled. One of the other issues with registry data is that we are unsure which type of antibiotic-laden bone cements are being used.

Commercially available cements are certainly faster to use in the operating room and may be mechanically superior to Surgi Made antibiotic-laden bone cements. However, they may also be less effective at eluting the antibiotic itself and do not allow for as much customization of certain variables such as cement viscosity or antibiotic type. Therefore, these differences make interpreting this data even more challenging and require the use of more strict prospective studies in order to make a clear and definitive answer.

And while I do not want to steal too much from Dr. Higuera's presentation, I do want to touch on the elution of antibiotics from antibiotic-laden bone cement as it relates directly to their effectiveness. In general, there is a large amount of elution of antibiotics from the bone cement in the first day or so. But again, this also depends on the viscosity of the cement itself, the antibiotic chosen, and various details related to the making of the construct in general.

As you can see from this slide, the variability of elution profiles of various cements has been evaluated in the past, and by the graphs on the right, you can see that the majority of the antibiotics is still released on the first couple of days. This release of antibiotics is important to consider when it comes to the eradication of infections, as the ability to remove bacteria and biofilm are directly dependent on both the concentration levels of antibiotics and the amount of time that concentration spends above both the MIC and the MBEC.

In short, the longer a cement can produce a local concentration of antibiotics above the MBEC, the more effective it will be. However, we do not currently have much data supporting the idea that we can provide antibiotic levels listed here for a prolonged period of time from antibiotic-laden bone cement constructs.

And what happens when all that antibiotic is gone? Well, the cement itself becomes yet another source in which bacteria can thrive or worse, possibly develop resistance.

While there are two institutional studies suggesting that resistance does not occur secondary to low-dose antibiotic cement constructs, there is one recent paper from the National Joint Registry suggesting that dual antibiotics should be considered if using a low-dose antibiotic-laden and bone cement in order to decrease the possibility of resistance to one or the other antibiotics. Taken as a whole, it does appear that antibiotic-laden bone cement may be able to play a role in both infection prevention and infection eradication. However, we lack the details necessary to make definitive conclusions.

And when it comes to safety and efficacy, it is also important to consider cost. Simply put, if we were to use antibiotic-laden bone cement on every patient, it would cost the healthcare systems around the world hundreds of millions of dollars each year. This is a staggering figure. And a recent study found that antibiotic-laden bone cement would need to be about 50 times more effective than plain bone cement at preventing infections in order to justify its cost for the use in primary joint arthroplasty. We certainly don't have this level of data to support the use at this time and until we do, the debate of when and how to best use antibiotic-laden bone cement will continue.

Thank you very much for your time.

DR. BERTRAM: Wonderful. Thank you, Dr. Krueger.

Just a reminder to our viewers, please feel free to submit any questions for the presenters via the e-mail provided: OHT6-FEEEDBACK@fda.hhs.gov.

Our next speaker is Dr. Carlos Higuera. Dr. Higuera completed his residency at the Cleveland Clinic and a clinical fellowship at Thomas Jefferson University Hospital. He specializes in hip and knee arthroplasty surgery. Dr. Higuera is currently a staff surgeon at the Cleveland Clinic Florida, where he divides his time between leadership, research, and patient care. He is the Chairman of the Levitetz Department of Orthopedic Surgery at Cleveland Clinic Florida and director of the Orthopedic and Rheumatology Center. The title

of his presentation is " PMMA Spacers: Effectiveness and Utilization."

DR. HIGUERA: I'm Carlos Higuera. I'm the Chairman of Orthopedic Surgery at the Cleveland Clinic Florida and I'm going to talk about cement spacers. Are they effective? Is there over-utilization to the detriment of patients in the treatment of PJI?

I don't have any disclosures related to this talk. Next slide.

Chronic periprosthetic joint infection treatment goals are to control the infection and to provide a painless and functioning joint. And it depends on surgical, organism, and different host factors. Next slide.

These are some treatment options, but we're going to talk specifically about one-stage or two-stage exchange arthroplasty, including the cement spacers to treat this condition. Next slide.

Now, I just want to be clear that cement antibiotic spaces are a very valuable resource in PJI treatment and I'm going to show you why. Next slide.

Let's talk first about hip antibiotic spacers that can be prefabricated versus surgeon custom-made. Next slide.

This is one of the first reports in the literature, almost three decades ago, that talks about how these spacers can provide stability to the joint while delivering local antibiotics. Next slide.

This is one current publication from our institution that showed some of those dynamic, functional spacers that actually can work almost as a primary joint replacement where the patient can walk and function on it. Next slide.

This is a review of the literature that basically just compares prefabricated versus surgeon-made spacers and does show that the pain and function after using this spacer improved significantly. I believe the only difference is that the spacer fracture is higher in surgeon-made spacers, but overall both are very successful. Next slide.

So this is a more recent review of the literature, almost 25 studies with a minimum follow-up at 2 years, that show that the control eradication of the infection, regardless of the type of spacer, is higher than 90%. Next slide.

Now, when we look at the knee antibiotic spacer and then we compare articulating versus static spacers. This is a study from Dr. Michael Morton *Journal for Arthroplasty* in 2014 that shows that dynamic spacers have better range of motion without compromising the control of the infection. These are very equivalent.

This is a meta-analysis that again, just showed very similar results, more recent, where the function is better with articulator dynamic spacers without compromising the eradication of the infection. Next slide.

This is an example of one of my cases where we use a static spacer in this case and the patient did really well after surgery. Next slide.

So in summary for this first part, there's really no difference on infection control and functional outcomes between surgeon-made spacers or prefabricated in the total hips. However, there are more fractures on the surgeon-made ones. Articulating knee spacers have better range of motion and function scores than static spacers, but there is equivalent control of infection.

Also, prefabricated spacers are more expensive and allow for less customization. And the reality is that no one fits all needs and every patient and case is different and requires a different type of spacer and attention to the detail makes a difference. And all this is based on the type of soft tissue coverage that we have available, and the bone stock. And basically, the surgeon made the decision based on this.

Now, this is another constant and is when we compare two stages when we use a cement spacer with one stage. This is a study from Kevin Bozic's group from 2019, where they did an expected value decision tree that was constructed using decision analytics,

measuring quality adjusted life-years and costs associated with one-stage versus two-stage, and they basically found that one stage was more effective and less costly.

However, just keep that in mind. When we compare one versus two-stage over the literature, there's really not statistically significant difference in infection rates. And the reality is there are very clear indications for one stage and the most important one is that we need to have a positive culture when we do one stage and that definitely had been reported in the literature and that has much better outcomes.

And in addition to that, if we have a resistant bacteria, this is one of the papers that show that only 18% success rate was reported with one-stage, if we include MRSA cases. These are other reports that do not necessarily include MRSA.

However, if we use some combination of high concentration antibiotics in the one, like sometimes they use different types of intra-articular Irrigation that reports, at least from some papers from China, improve the control of the infection.

The advantage is when we compare these to two stages compared to one stage, is that we have good debridement and have good midterm results and it's very reproducible. However, it's more costly, there is some morbidity with the spacer, it takes longer and some of the function and the patient satisfaction is less.

This slide just shows in a nutshell what we do when we do an explant and a cement spacer placement.

And overall, the success of two stages is about 80 to 90% across the literature. It depends on what definition of success do you use for that. However, when we have resistant bacteria, unfortunately, this success rate drops significantly.

And this is one of the recent publications for the Rothman group that basically shows that despite all of our best efforts, if we include all comers using two stages, the overall success rate at 2 years is about 65% and almost 20% of patients did not receive a

reimplantation.

So in summary, chronic PJI is a devastating complication after total joint arthroplasty; unfortunately, still with suboptimal treatment results. Spacers are effective; however, they have limitations. Two-stage revision is like two one-stage revisions, but both have different and unique indications. There is definitely no over-utilization of antibiotic spacers, and due diligence on the surgical technique and tailoring of antibiotics can make a difference. Thank you.

DR. BERTRAM: Thank you, Dr. Higuera, I appreciate your insights.

Our next speaker is Dr. Stuart Goodman. He received his bachelor's, master's, and medical degree from the Institute of Medical Science at the University of Toronto, and his Ph.D. in orthopedic medical science from Lund University in Sweden. He is a Robert L. and Mary Ellenburg Professor of Surgery, and professor with tenure in the Department of Orthopaedic Surgery at Stanford University. Dr. Goodman has a courtesy appointment in the Department of Bioengineering and is a fellow of the Institute of Chemistry, Engineering and Medicine for Human Health at Stanford University. He is a fellow of the Royal College of Surgeons in Canada, the American Academy of Orthopaedic Surgeons, and the American College of Surgeons. The title of our next presentation: "Current Evidence Regarding Device Coatings."

DR. GOODMAN: Thank you for the opportunity of speaking at this symposium.

The human body has undergone some dramatic changes with the introduction of new implant technologies.

The reaction to implants placed in the body is dependent on host characteristics, the anatomical location, implant characteristics, surgical technique, the mechanical environment, the presence of infection, and other factors.

Even a previously osseointegrated implant can loosen when bone is lost due to

ongoing chronic inflammation and infection.

In this example, polyethylene particle disease and chronic low-grade infection caused progressive bone loss, pain, and poor function of a hip replacement, necessitating two-stage surgery.

As Tony Gristina stated, when a prosthesis is implanted, there is a race for the surface between local host cells and bacteria.

Furthermore, degradation products from implants can harbor bacteria on their surface to cause adverse local and systemic tissue responses.

Implant infection has a substantial financial and societal burden, as seen on this slide.

Thus, there are great opportunities for implant coatings to mitigate implant infection; however, the coatings must fulfill numerous criteria to establish their safety, efficacy, and cost-effectiveness. These criteria are listed on this slide and emphasize the enormous effort that is necessary to garner regulatory approval and clinical acceptance.

Different classifications have emerged including the one outlined here, in which coatings can be passive or active surface finishings or modifications applied to the implant in advance versus those applied at the time of surgery.

Coating strategies to combat infection include interference with bacterial adhesion, proliferation, biofilm formation, and eradication of planktonic bacteria.

Here is one example. Silver byproducts compromise the bacterial membrane and interfere with the intra-articular machinery to make DNA and key proteins.

In another example, antimicrobial peptides, or AMPs, on the implant surface can function as bactericidal agents or immunomodulatory molecules.

Let's examine titanium surfaces to elaborate the different opportunities to prevent infection with coatings. The different strategies are listed on this slide. Let's look in more

depth.

Different antibacterial moieties can be grafted onto the surface or functionalized using the titanium oxide layer. Anodization of the surface can produce nanotubes that facilitate tissue formation and discourage bacteria on the surface. Layer-by-layer coatings, seen on the right, can include different agents such as antibiotics.

PolyNIPAM surfaces that swell and contract can prevent bacterial adhesion. Exposure to UV light or surface treatments by AMPs, antiseptics, ions, etc., can also be effective.

There has been a plethora of in vitro and in vivo preclinical studies examining different implant coatings. However, there have been few high-quality human studies published in the literature.

A recent systematic review and meta-analysis concluded that gentamicin, silver, and povidone-iodine coatings were associated with decreased infection rates. The data from this study are shown on these forest plots, clearly establishing efficacy.

Anodic oxide-iodine film coated implants were shown to be particularly successful in preventing infection in large tumor surgeries.

Intraoperative methods to apply an antibiotic-loaded hydrogel have shown promise in studies of cementless revision hip replacement.

Our work has centered on the use of chemokines for immunomodulation of the local environment in and around bone. In one project to prevent periprosthetic osteolysis, we used a layer-by-layer technique to release a mutant MCP-1 protein, called 7ND, to prevent pro-inflammatory macrophages from trafficking to the area of excessive wear particle production.

Comprehensive in vitro and in vivo studies have validated this concept. This technology can be modified to prevent and treat infection by varying the molecules in the

layer-by-layer coating.

So what is the forecast for the future? Some of this information is in an a prior publication of ours. However, we must always be focused on specific goals and formulate strategies to attain these goals.

In another publication we emphasize the fact that coatings in the future will be multi-functional, for example, to both promote osseointegration and prevent or treat infection. These coatings should be targeted and directed, demonstrate a high level of safety and efficacy, be user friendly, and cost-effective. For example, here is one local dual delivery system that dispenses silver and strontium ions from an implant surface to both combat infection and facilitate osseointegration by polarizing macrophages from an M1 to an M2 anti-inflammatory, pro-reconstructive phenotype. This dual delivery method has been validated by extensive in vitro and in vivo studies.

Finally, future smart coatings will not only be functional at initial implantation, but may contain surface receptors and sensors for late activation of putative treatments.

Thank you for the opportunity of presenting this information to our colleagues at the FDA and other listeners.

DR. BERTRAM: Dr. Goodman, thank you very much for your insights and forward thinking.

Our next presenter is Dr. Noreen Hickok. Dr. Hickok obtained her Ph.D. degree in physical and inorganic chemistry from Brandeis University. She is Professor of Orthopedic Surgery and Biochemistry and Molecular Pharmacology at Thomas Jefferson University in Philadelphia. The title of her presentation: "Current Evidence for Surface Modifications of Arthroplasty Devices."

DR. HICKOK: Good morning. I want to start by thanking the organizers for this opportunity to speak and for making this conference possible.

As you can see on the next slide, I have no financial conflicts of interest to report.

On the next slide we see a representation of three general ways to attack infection associated with -- implanted material. Traditionally, we focus on defense lines two and three, antibiotic usage to eradicate bacterial contamination. However, we have always reasoned that the best place to attack the problem is by surface modifications to prevent bacterial adherence.

In the physiological environment, if such a surface could be created, it could well remove the implant from the contamination equation and move the situation back to the contamination that traditionally can be handled by antibiotics and the immune system with limitations, of course. Next slide.

So as we have thought about the questions of how to best modify surfaces for use on orthopedic devices, we find ourselves needing to answer these six questions. I put the reduction in surface colonization first, as that is the true success criteria. These, of course, are not the only questions. These modifications of a surface must exist in a mechanically dynamic environment that is subject to the insertional and modeling stresses associated with orthopedic hardware. So the last question touches on this mechanical fallout and it's the reason that I don't showcase the very powerful soft material systems that have been created. Next slide.

The most satisfying way to engineer a mechanically robust surface is to use the implant material itself to innately confer antimicrobial activity or to imbue them with structures that affect bacterial adhesion. The micrographs I show compare bacterial morphology on a flat Ti surface in the upper left micrograph versus natural surfaces such as dragonfly wings that are antimicrobial.

In the process of trying to adhere to the surface, the bacteria need to undergo shape changes that are incompatible with their function, resulting in bacterial death and of

course, analogous nanostructure materials have been designed. Similarly, material composition itself may affect bacterial adhesion and we see small changes in bacterial adhesion between the different metals used for orthopedic implants. Overall, these surfaces are probably inadequate as they usually are only able to reduce bacterial colonization by one to two logs in vitro and for the nanostructures may be too liable to removal during the insertion process. Next slide.

We and others have explored how best to use the surface to present antimicrobial concentrations of antibiotics. Many years ago, Jay and I spearheaded the covalent modification of Ti surfaces with vancomycin, which was followed with the tethering of antimicrobial peptides. There's synthetic analogs and antimicrobial polyamines among many others.

The picture on the right shows the direction taken by Oral and her group at Harvard who eluted therapeutic concentrations of vancomycin while having vancomycin remain in the UHMWPE matrix to render that part of the implant permanently antimicrobial.

Silver is, of course, the poster child for a substance, which both renders the surface antimicrobial and through elution kills non-adherent bacteria. In vitro studies, animal model, and in vivo data remain fairly out of sync with cautionary tales from other fields such as urology where silver-eluting catheters may not cause a significant enough decline in bacteremia to justify their cost. Whether distinct silver nanoparticles result in acceptable cost-to-efficacy toxicity ratios remains to be determined overall.

However, the take-home message is that with these antimicrobial containing systems, sufficient activity may be present or eluted to present some possibilities for development. Next slide.

In all of the slides I've included the approximate reduction in surface-bound bacteria, but is it enough? It is unlikely that any by themselves will ever result in complete

eradication.

In this slide, I have reproduced the radiograph, the micro CT, from Tom Schaer paper testing permanent bound Ti surfaces in a sheep model of infected osteotomy. It is quite evident that complete bone healing occurred over 3 months with the VAN displaying plate, whereas the control showed lack of healing. These surfaces were only able to reduce adherent bacterial counts by about one to two logs with a tinted sixth inoculum in vitro, but clearly with the immune system were sufficient in vivo. My rule of thumb is to aim for about a three log decrease, that is where I am comfortable, but Tom's data clearly raises the question of how these in vitro log reductions correlate to outcomes. So frankly, we don't know what is required, and I suspect it is different depending on the application and system. Next slide.

Of critical importance in these surfaces, however, is their ability to foul. The nanostructured surfaces are particularly prone to this problem as the absorbed serum proteins start to average out the structure that has been engineered into the surface. Importantly, the natural analogs of these surfaces all have means to regenerate, whereas the surfaces and implants are static.

In terms of other surfaces in our hands, our permanently modified surface was not affected by protein fouling, although it's easy to imagine that permanent brush-like surfaces would not be that resilient. Clearly the surfaces most unaffected by surface protein coverage are likely to be the eluting surfaces. Next slide.

An equally important unknown in our calculation is what duration of activity is required. Recent studies suggest that the idea that longer is better may not in fact be correct, but we don't know about the bone environment. We do know that perioperative antibiotics over the first 24 hours are important. For longer than 24 hours, it's not suitably supported. For active infection, most dilution systems maintain above MIC levels for long

periods. Next slide.

Specifically, this table is borrowed from a review paper looking at different antibiotics measured during the elution. Given that the MIC for VAN for methicillin sensitive to *S. aureus* is 1 to 2 μg/mL and -- below 1 μg/mL, these systems all achieve many times greater than the MIC at 24 hours. By 7 days, the drop is 3 to 10-fold, but antibiotic levels are still well above the MIC. Next slide.

But as is shown by looking at in vitro data, which is shown in this slide, MSSA biofilms on the biomaterial peak require a greater than 100 μg/mL of vancomycin in human synovial fluid for eradication after 24 hours. So some elution systems reach these levels in the first 24 hours. It's a question of how much and how long are interrelated. For elution systems, this is still a changing target which needs to be pinned down, especially when we speak about prolonged dilution above MIC. Again, as is shown here, MIC levels are unable to touch biofilm bacteria.

On a different note, for the permanent surfaces, the amount of antimicrobial activity should be defined as the density, and the MIC is not meaningful in this context. We don't know what these concentrations are. In all of these applications, as we reach the necessary concentrations, we need to ask about toxicity. Such studies are starting to be performed in animal models looking at inclusion of large amounts of vancomycin powder. Next slide.

The ability of antimicrobials to defeat bacterial contamination can be dependent on the number of bacteria. Currently, very high concentrations of antimicrobial are used for a short duration in prophylaxis. In vitro data would suggest that this is probably the right approach. The question of treatment of established infection is, I think, still not known, as current treatments are able to ostensibly sterilize the joint, but reinfection rates are high suggesting that the physiology of the joint may be hampering treatment, whether through sequestration of tissue-bound bacterial aggregates or the chronic infection associated with

bacterial ingress into the bone matrix. Next slide.

These questions of how much and how long, at least for the uncemented implant, are taken care of in the permanent surface antimicrobials. Unfortunately, in the process of making the permanent antimicrobial, the starting antibiotic may be modified, albeit the mechanism remains the same so as to cause it to be classified as a new drug with unknown toxicity when it is released as it inevitably will be. Next slide.

So where are we with my questions? As always, I feel like it is very difficult to nail down the individual answers, especially some of them are clearly interrelated. We know that we can make model implant surfaces that reduce surface colonization and our sheep study suggests that in the presence of a robust immune system about two-log reduction may be enough.

We also know that any surface will be rapidly coated by serum proteins, which may mask the underlying surface. This seems to be the most important for topographic modifications, where other modifications may be less severely impacted.

We still don't know how much and how long we need the antimicrobial around, while it is probable that the answer will be different depending on the application. Next slide.

Finally, I want to acknowledge the funding entities that have supported the work performed by Jay, by Tom, and by me over the years. Next slide.

And even more importantly, the people whose work has informed my thinking about joint infection. Thank you for your attention.

DR. BERTRAM: So that concludes our presentations for Session 2. Dr. Hickok, thank you very much.

Now it's time for our presenter discussion. Our moderators for this discussion will be Dr. Javad Parvizi and Dr. Edward Schwarz.

As previously introduced, Dr. Parvizi is a board certified orthopedic surgeon and has been at the Rothman Institute since 2003, specializing in the management of young patients with hip disorders.

Dr. Edward Schwarz is the Burton Professor of Orthopaedics and director of the Center for Musculoskeletal Research at the University of Rochester Medical Center in Rochester, New York. His laboratory focuses on inflammatory bone loss such as that seen in rheumatoid arthritis, infections, tumor metastasis, and wear debris-induced osteolysis around loose prosthetic implants. Dr. Schwarz is also a leader in orthopedic biologic therapy and stem cell research for which his lab has developed a novel passive immunization for MRSA and revitalizing allograft approaches for bone and tendon regeneration.

Moderators, please take it away.

DR. PARVIZI: Thank you, Dr. Bertram.

And thanks to the speakers, they did an amazing job talking about complex issues in that small time interval, thank you. We're exactly on time and we're doing great and so far, everything's going well.

Eddie, I will let you start with the lineup questions for the speakers, if you don't mind.

DR. SCHWARZ: Sure. So Question 1 is the combination of oral antibiotics and antibiotic cement spacers that would be a concern for systemic toxicity. Do each of the panel members have the typical oral antibiotic prescription for use with antibiotic spacers?

DR. HIGUERA: Thank you very much again for the invitation. Well, the reality is we measure some of the antibiotics and the typical case is vancomycin, for example, where we use systemic vancomycin and most of the time this is IV at the same time that we use a spacer. It is very rare that we currently use an oral antibiotic in combination with a spacer.

For the most part, the use of a spacer relies mainly on the acute phase of the treatment when we -- probably 90 to 100% of the time we use IV antibiotics and not oral.

Again, we use measurement of systemic levels of the vancomycin and we adjust as necessary as, you know, it depends on a lot of different variables like renal clearances and weight of the patient, etc., and depending on that is how we adjust these dosages. And it is important to understand that there is no way that we have currently on patients to measure the elution of the antibiotics and therefore, we cannot combine the adjusting of the systemic use of antibiotics with whatever is being eluted by the spacer.

DR. SCHWARZ: Great. So I would say that that also addresses the second question we have in terms of how we're monitoring that. I don't know if you'd care to answer the third one which is, is there a preferred combination of antibiotics used for addition to bone cement and cement spacers?

DR. PARVIZI: And if it's okay with you, Eddie, I would like to combine that question with another one I had for Yale. So Yale, very compelling study that shows there is no efficacy for antibiotic-impregnated cement, at least not during primary total hip arthroplasty or total knees. And it's very important to mention that antibiotic-impregnated cement has not been cleared for the use during primary, so that's an off-label use of the combination.

In your opinion, which antibiotic is most likely to be efficacious, in the antibiotic, if used during a primary and would the combination work better? And if so, should we limit this to high-risk patients or do you think there is enough evidence to try to justify its use in all primaries?

DR. KRUEGER: I don't know if Yale's on. I can handle that question, though. So in terms of which antibiotic I think may be more -- most efficacious, a more broad spectrum one such as like a tobramycin, which is commercially available as well, you know, that's

typically what we use in spacers that a lot of us are constructing for these infected joints, as well. So you try to find some type of broad spectrum that has an elution profile that we may understand, at least to a degree.

At the same time I certainly can't say that using a gentamicin or daptomycin is specifically any worse than a tobramycin, either. So some of it may come into play in terms of if someone had a previous infection, which would obviously be a high-risk patient, making sure whatever antibiotic we're using would cover that drug, if you're going to use that during a primary joint would be beneficial.

And just to piggyback on Dr. Higuera's point earlier, as well, in terms of oral antibiotics, I know there is some literature coming out suggesting maybe they could be useful in high-risk patients postoperatively and again, we wouldn't be able to measure that in terms of how much antibiotic we would be giving orally in addition to what load you place into the cement if we're going to use those in a primary fashion. Most of the cements do have a relatively quick elution where most of the antibiotic is eluted within the first week or so. That being said, some of that does depend on what cement is used and also the amount of cement used. Someone with a smaller femur getting antibiotics in their cement may have a different level of the drug than a larger femur, and that doesn't always correlate to the size of the patient.

DR. PARVIZI: Thank you, Chad.

DR. SCHWARZ: Excellent. Maybe I could ask the next question to Dr. Goodman, which is really the balance of the bactericidal activity of these combined drugged implants and then the transition to the osteogenic phases in which they have to be friendly to fibroblasts and chrondocytes. Where is this balance and how do we consider this in terms of FDA approval and metrics for assessing them? You're on mute, Stuart. Sorry.

DR. GOODMAN: Thank you, Eddie and Jay and the FDA. I apologize for the lack of a

tie, but I'm doing surgery shortly, so I'll try and be brief.

This is a very complicated situation because on the one hand you want to prevent infection or treat infection, and on the other hand you don't want to have any bystander injury to the cells that we need to stabilize that prosthesis. And I think we have to begin with clearing that infection and I think timing is going to be of great importance. So it's great to think of doing both at once, but the fact of the matter is, I think that clearing the infection, the bacteria, the byproducts from macrophages and PMNs and lymphocytes, they're not only going to sustain the infection, but they're going to limit osseointegration. So I think dealing with the infection first and at the appropriate time period yet to be determined, one has to facilitate osseointegration, decrease osteolysis, and hopefully get an interface that's going to be stable long term.

DR. SCHWARZ: If I could over-interpret the question and simplify it, would you imagine that these clinical trials for these combination products would actually have two primary outcome measures, an initial primary outcome measure for infection and a secondary outcome measure for osseointegration or fracture healing?

DR. GOODMAN: I think that's a good idea. I think that it all starts with preclinical research to get the right combination, the right timing, and then I think I agree that one's going to have to look at eradication of the infection, as well as outcome studies looking at how these implants perform clinically and that would mean clinical studies of outcome and also imaging studies, as well.

DR. SCHWARZ: Could I ask the ask the next question to Dr. Hickok, which is combining a number of these in the channel where we're going now towards into cost-effectiveness questions. We have wonderful sophistication that we're adding to these things, but adjudicating that and understanding how that's going to be reimbursed in the end, where is that in the thinking of the field, I guess, are really the questions I see in the

chat.

DR. HICKOK: Yeah, I mean, the cost is an interesting question but I know that Jay and I went through a whole costing back in the days when we were chemically modifying implants and surprisingly, the addition of cost was trivial. So I think that the quality control aspects of it may be the most costly as opposed to the actual modifications themselves.

I mean, Jay, do you have anything to add to that?

DR. PARVIZI: Oh, I agree, Noreen. It completely obviously depends on what technology we use, but it should definitely be very cost effective.

Eddie, a question came through and I know, Dr. Bertram, we're running out of time, but it's a very important one and a very big challenge for the Agency right now. The question that's come through is are there any efforts to fight infection biologically, meaning using DNA/mRNA therapies to fight infection similar to the vaccine or targeted cancer therapy?

I want to make a plug here for phage therapy. I just put a patient of mine through phage therapy. I saw him at 3 months. He had multi-resistant organism, he'd had 11 prior operations and had failed, and he's one of the happiest people right now. So phage therapy has been around for a long time. We did seek FDA approval, but I must admit, it was an incredibly arduous and very, very long and drawn-out process. Not just because of paperwork at the Agency, but also because of paperwork internally, etc.

So I want to leave all of us with the thought that should we, in the day and age where we are having a real issue with antibiotics and efficacy of a lot of these agents we're using on a daily basis, the systemic toxicity that Bryan talked about, etc., has the time come for us to go and visit a 1915 technology that's been around for decades and perhaps utilize something like that in our patients? I know Dr. Gina Hsu, who was at Stanford, Stuart, as you know, is not at Mayo Clinic, she has also enrolled quite a few of her patients into phage

therapy and there are others that are doing it.

So yes, to answer that question. And of course, this is my personal opinion, I think the time has come that we need to use biologic methods to fight infection and that does include us giving phage a serious consideration.

DR. SCHWARZ: So I guess I would love a chance to answer that question, starting with really the enormous precedents that are being currently set with the COVID-19 Warp Speed program and the -- hopefully the transparency that will come from that. We know that compassionate use has been extensively used during this pandemic. We also have heard in the lay media that thresholds for approval, such as 50% efficacy of the vaccine, is being considered. And so I think a major question will be how many of these historical precedents being set by this pandemic will transcend to all areas in medicine, including antimicrobials in orthopedics.

And I think your question is excellent with respect to archaic therapies. Again, in the COVID pandemic where we have the investigation of two, the hydroxychloroquine, which turned out not to be good, but then steroids, which is equally as archaic, turned out to be probably the best thing we have now for treating these patients with serious infections.

And so the challenge really is to understand this new mechanism of compassionate use and enabling doctors to consent their patients properly and then based on that experience, design efficacy trials, safety and efficacy trials.

DR. BERTRAM: I have to say this is another great conversation and great insights and I also can't stress how easy you're making my job, right on the dot, 10:10, keeping the show moving. But again, really great and appreciate everyone's insights into this.

This brings us to the end of our session, it brings us to break number two. Like I said before, see you in 5 minutes.

(Off the record at 10:10 a.m.)

(On the record at 10:15 a.m.)

DR. BERTRAM: Welcome back to Session 3, everyone. Session is titled "Orthopedic Trauma Devices: Knowledge Gaps and the Development of Device Technologies to Address Unmet Needs."

Our first presenter is Dr. Michael Bosse. Dr. Bosse graduated from the U.S. Naval Academy in 1974. He completed his medical school at the University of Maryland. He received his training in orthopedic surgery at the Naval Hospital in San Diego and became the first formal military orthopedic trauma surgeon after completing a trauma fellowship at the Baltimore Shock Trauma Center in 1984. At present, Dr. Bosse is an Emeritus Professor of Orthopaedic Surgery at Atrium Health Musculoskeletal Institute in Charlotte, North Carolina. He is a past president of the Orthopaedic Trauma Association, and is the Emeritus Chair of the Major Extremity Trauma Research Consortium. Dr. Bosse's presentation is titled "Evidence Gaps and Emerging Solutions for Use in Acute Orthopedic Trauma."

DR. BOSSE: I am Michael Bosse and I will present thoughts on critical knowledge gaps and emerging solutions for use in acute orthopedic trauma care. Slide Number 2.

Infection is not an uncommon problem in the care of closed complex fractures or open fractures. Reported infection rates range from 1 to 30% for closed high-energy pilon, tibial plateau, and calcaneus fractures. Fracture-related infections worsens the patient's outcome and are expensive, doubling the cost of care in one recent study. Slide 3.

The infection data is even more dismal for open fractures. Our established open fracture protocols require that all high-energy open fractures are treated with early debridement and an initial burst of broad-spectrum antibiotics. The wound bioburden through the course of care is rarely defined, therefore, generally unknown. The type and duration of antibiotics employed at the time of wound coverage remains empiric and is usually provided for only 24 hours. And lastly, the optimal timing of wound closure or

coverage is unclear, and the risk of a nosocomial colonization is probably related to the time to final wound coverage. Slide Number 4.

This approach has provided consistent results for the Type III tibia fracture over the past quarter century, a 25% deep infection rate. Pathogens recovered at the time of infection surgery are trending to gram-negative rods, MRSA, *Enterococcus*, among other species. These bacteria are usually not targeted by the antibiotics provided at the time of the wound closure surgery.

Our unchanged 25% tibia fracture infection rate is concerning. Continuing to use the same open fracture care tactics we've employed for the last 25 years is unlikely to result in different outcomes over the next 25 years. It's time to change things up. Slide 6.

Biofilm remains an unsolved problem. If bacteria are present in the wound or surgical site, we need to prevent the bacterial adhesion to the tissues and implants, prevent the initial biofilm production, and have the ability to disrupt or eliminate any established biofilm colonies. At the time of wound closure or coverage in the care of the closed or open fractures, ideally, we will have a sterile tissue bed. Slide Number 7.

An equal or greater challenge is to recognize that the bacteria can enter and survive inside the osteocyte protected from all current antibiotic strategies. Shown is a case of chronic osteomyelitis from a prior open fibular fracture. Samples from the debridement were studied by routine and electron microscopy, and intracellular bacteria were noted in most or many of the cells. Future research might target cell mechanics to prevent invasion or cell membrane-crossing therapeutics to target the intracellular bacteria. Slide Number 8.

Host and injury factors combined determine the risk level for fracture-related infections. Non-modifiable host factors include the severity of other injuries and the care they require, and the patient's smoking history, obesity, diabetes, and other pre-existing conditions. Unlike elective orthopedic surgery, acute orthopedic trauma cases have

compromised tissues and regional blood flow and if open, have environmental hosts and nosocomial contaminants. Slide 9.

In the care of closed fractures, treatment opportunities are focused on the prevention of bacterial colonization of the surgical site. There are some promising new strategies to minimize colonization and subsequent implant adhesion, biofilm production, and late infection. Slide 10.

Local antibiotic therapy is not a new concept and was first used in World War II. There are promising single-center fracture studies that showed efficacy for surgical site application. This low-tech therapy, if effective, could have a major impact at a very low cost. Slide 11.

Our recently completed multicenter, prospective randomized trial of almost 1,000 patients compared local vancomycin powder to standard of care enclosed and low-grade open high-risk tibial plateau and pilon fractures. The sample was appropriately sized and the cohorts were well-matched. Slide Number 12.

The study reported a significant reduction in deep surgical site infection related to gram-positive bacteria. No effect was noted for gram-negative bacteria. Slide 13.

This finding begs the obvious question: What impact would a combined therapy, vancomycin plus tobramycin, have on the fracture-latent infection rates in this series? This combined local antibiotic study is to begin enrollment early in 2021. Slide 14.

There are some data to suggest that high-dose perioperative oxygen can reduce the infection risk by increasing the bactericidal activity of host neutrophils. This therapy is cheap and readily available but needed a large multicenter, prospective randomized trial to prove efficacy and value. Slide Number 15.

Our prospective, randomized, multicenter, over-1100 patients trial was recently completed to study the effect, if any, in surgical site infection reduction in high-risk

fractures of the tibial plateau, pilon and calcaneus, if exposed to high-dose perioperative oxygen therapy. Again, the treatment groups are appropriately sized and similar. Slide 16.

The study showed a reduction in the surgical site infection rates at all time points. Slide 17.

Implant coatings or surface modulation techniques are other important emerging technologies and will be addressed in a later presentation. Slide 18.

As already argued, the care of the high-energy open fracture needs improvement to reduce the unacceptably high fracture-related infection rate. We need new strategies to eliminate or minimize wound colonization, to better understand the terminal wound bioburden, to develop targeted patient-specific systemic antibiotic therapies that are coupled with local antibiotic applications, and we need a better understanding of the earliest optimal time for complex wound closure or definitive wound coverage. Slide 19.

A prospective observational study was completed in 655 open tibia fractures in order to define the terminal wound bioburden at the time of soft tissue coverage or closure. At the time of closure of these complex wounds, there was a 30% positive culture rate. Coag-negative *Staph*, *Enterobacter*, *Enterococcus*, and *Serratia* were the predominant bacteria. Slide 20.

An infectious disease panel rated the effectiveness of the cultured bacteria related to the antibiotic selection and duration provided to each of the culture-positive patients. The therapy was rated as effective, likely effective or ineffective against the recovered bacteria. Slide 21.

Forty-eight point seven percent of the antibiotic therapy provided at the time of wound closure or coverage was judged to be not likely effective in the treatment of the wound bioburden. Slide 22.

In summary, for the care of the high-energy open fracture, there are no guidelines

directing the type and duration of antibiotics at the time of wound coverage or closure. The terminal wound bioburden is not as expected. Coag-negative *Staph*, *Enterobacter*, and *Enterococcus* are common pathogens. The antibiotics employed were effective only 51% of the time. We clearly don't know what we're doing. Slide 23.

An appropriately powered, multicenter, prospective randomized trial is needed to test a combined targeted systemic and locally antibiotic therapy in a Type III tibia fracture to the current standard of care. Enrollment in this study will begin next spring. Thank you.

DR. BERTRAM: Thank you, Dr. Bosse.

Again, please feel free to submit any questions for the presenters via the OHT 6 feedback e-mail.

Our next presenter is Dr. David Lowenberg. He is Clinical Professor of Orthopaedic University at Stanford University School of Medicine and served as the chief of the Orthopaedic Trauma Service at Stanford from June 2010 until January 2016. He is a past president of the Limb Lengthening and Reconstruction Society of North America, past president of the Foundation for Orthopedic Trauma, and immediate past president of the Osteosynthesis and Trauma Care Foundation International. He is also co-director of the Buncke Microsurgical Research. The title of his presentation is "Evidence Gaps and Emerging Solutions for Use in Chronic Osteomyelitis".

DR. LOWENBERG: Thank you. This talk will summarize the current obstacles in the treatment of chronic osteomyelitis and the potential opportunities for treatment in the future.

I have nothing to disclose.

This pie chart represents the breakdown of my current practice. As over 50% of nonunions are probably infected or at least colonized, 60% of patients I treat have some component of chronic osteomyelitis.

Some would say that treatment involves a battle between us -- eukaryotes -- and them -- prokaryotes -- but this is not a battle that we can wage as we are truly a biosphere that is as dependent on them as they are on us.

When one measures the number of prokaryote to eukaryotic cells in any one of us, it has been shown that the ratio is 10:1. When one measures the number of viral particles to prokaryotes in our biosphere, again, the ratio is 10:1. This leaves a viral particle to us ratio of 100:1. Looking at the number of genes this represents, there are 400 microbial genes for each human gene in our body. Hence, a mindset of trying to better get along is probably a healthier way of trying to deal with this infection problem in the future.

Several research groups have measured the free-floating nucleic acids in our plasma. It is a humbling fact that over two-thirds of the free-floating DNA and RNA segments are of viral origin. This shows how truly intertwined we are with the microbial world. Therefore, I firmly believe that to treat such infections we must first precisely understand the behavior of the microbes involved.

The planktonic cell phase of infection. These are cells that are young with a rapid metabolic rate and rapid generational cycle. This is the cell line responsible for acute infection and is the cell phase most susceptible to antibiotics.

The sessile cell phase. This represents the semi-dormant cell phase of bacteria, which makes up roughly 98% of any biofilm colony and is the hallmark of a chronic phase of infection.

Biofilm. As the bacterial colony gains a foothold and begins its transformation to a sessile cell predominance, a biofilm is meticulously constructed. This highly organized matrix represents a long-term hydrophobic home to the colony and represents another blockade to antimicrobial penetrance.

Another contributing factor to the development of microbial antibiotic resistance is

the cell line's generational cycle. The planktonic phase has a generational cycle of under 30 minutes, while the sessile phase is closer to a day. This is in sharp contrast to humans where that figure is 20 to 30 years.

This slide summarizes the key differences between these two primary cell phase lines. It is important to note that these differences lead to a difference in susceptibility to most antibiotics of about 1,000-fold between them.

When looking at how fast antimicrobial resistance can occur in the real world, it is a sobering fact. Perhaps one of the best examples is linezolid. This is a completely synthetic antibiotic and no microbe had ever been exposed to this before the late 1980s. It was licensed in the UK in February of 2001 and by October of that year resistant strains were being reported.

What further complicates our ability to treat these infections is our limited ability to even isolate microbes. We rely on culturing techniques, which are now 150 years old. A panel of microbiologists reported that to their best estimates, we can only currently culture about 1% of the microbes believed to be on our planet.

To confound this further, roughly five years ago new forms of facultative prokaryotes were isolated. These have been called ultrasmall microbes. They are capable of passing through filters we previously thought were sterile.

Currently, we rely predominantly on antibiotics to treat our infection problems. In 2014, a CDC panel reported on the usage of antibiotics in the United States. The results were shocking. Fifty-one tons of powdered antibiotic were consumed in the United States per day. Although 70% of this usage was in livestock, poultry, and fisheries, a staggering amount was and is being used in humans. We are clearly not winning the battle with this approach.

The London School of Hygiene & Tropical Medicine has predicted that worldwide by

2030, this number shall increase to 105,600 tons per year. This equates to 290 tons per day dumped into our atmosphere.

Deaths attributable to multi-drug resistant microbes have been predicted to increase sharply over the next 30 years. By 2050, this has been predicted to represent a leading cause of death in the world, surpassing cancer and diabetes.

From what we know then, the only effect systemic antibiotics have on microbes in a biofilm that are in a sessile phase are to suppress the release of colonizing planktonic cells into the host. The antibiotics induce a Pavlovian response, if you will, in the biofilm inducing the cessation of the planktonic shedding and induction of other mechanisms in the biofilm colony to create and attain resistance to the antibiotic.

So intravenous antibiotics and long-term antibiotics, what is their role in the treatment of chronic osteomyelitis?

I have given variations of this talk throughout North America and Europe and always ask the same question, at your institution what percentage of your patients with chronic osteomyelitis are treated with long-term intravenous antibiotics? At virtually every institution and event that I have asked this, the answer is always the same, between 75 and 100%.

We studied 164 consecutive patients with chronic osteomyelitis who did not require chemotherapeutics for other infectious issues with an isolated focus of infection that had 2-year follow-up. One hundred and twenty-seven patients composed this study group. The demographics show a preponderance of males and a mean and median age in the mid-fifties.

As would be expected, the most common site was in the lower extremity. Surgical treatment did not change and was based on the principles of good osteomyelitis surgery to include thorough debridement and dead space management followed by reconstruction.

Only seven patients received an extended course of antibiotics. These patients were immunosuppressed secondary to autoimmune disease and its associated treatment, or due to active cancer or cirrhosis. The other 120 patients received three or less days of intravenous antibiotics and up to a week of oral agents.

At 2 years there were only two treatment failures with recurrence, with one of these then cured with a wider resection and bone transport. At 3 years, one more patient recurred with a total of three recurrences at 3 years. This gave a single round intervention cure rate of 97.6% at 3 years.

Moving forward, I feel we need to focus on two specific areas to improve future care. The first involves improved testing methods for bacteria. The most promising remains direct DNA testing for bacterial genetic material from tissue samples. This will improve the yield for microbes in a sample and pick up microbes in a sessile cell phase that currently do not grow on culture media.

Improved treatment modalities include better local antibiotic delivery methods. This would include the use of dead space void fillers that allow a sufficient concentration of antibiotic to be eluted to achieve efficacy against the sessile cell phase.

There have been strides made with short-chain RNA messaging to the biofilm to go into a permanent state of sleep, thereby creating a homeostatic and symbiotic state with the host without disease progression. This presently looks like the most promising long-term solution.

Phage therapy also shows promise but will require a great deal more work in basic science for a better understanding.

Biofilm disruption technology has been plagued with problems, with the most frequent being high immunogenicity by the host to these agents. Hopefully, this can be overcome with time.

Lastly, creating new and more powerful antibiotics does not represent a prudent and lasting way of dealing with this problem due to the reasons outlined in this talk. Thank you.

DR. BERTRAM: Interesting. Dr. Lowenberg, greatly appreciate it. And just a reminder, keep the questions coming in, great to hear from you.

Our next presenter, Dr. Tracy Watson, is currently Professor of Orthopaedic Surgery and the chief of the Orthopaedic Trauma Service at Saint Louis University School of Medicine. Dr. Watson received his bachelor's degree in zoology and physiology from the University of Wyoming. He completed medical school at Creighton University and then his orthopedic surgery residency at the Cleveland Clinic. This was followed by a trauma fellowship at the University of Texas Health Science Center, Parkland Hospital in Dallas, Texas, and then completed two A/O traveling fellowships in St. Gallen, Switzerland and Munich, Germany. He is a past president of the Orthopaedic Trauma Association, and recent chair of the Committee on Biologics and Regenerative Medicine for the AAOS, serving in that capacity from 2015 through Jan 2020. The title of his presentation: "Biodegradable Delivery Systems."

DR. WATSON: Thank you very much.

Local antibiotic application is the ultimate biodegradable delivery system. It's generally considered safe, but does have a potential for toxicity. This is primarily a dose-related issue, however.

Good recent data from the METRIC Group using local delivery and closed fractures demonstrates a significant decrease in gram-positive as well as gram-negative infection.

A recent meta-analysis also evaluated local antibiotic use in open fractures and found an 11.9% risk reduction for use in open fractures. Last year, the ICM also looked at this and found a four times reduction in infection rates for all grades of open fractures.

The standard delivery mechanism currently, however, is bone cement and does have

the advantage of many potential delivery systems. However, it offers limited elution characteristics and obviously requires removal. It does have ease of application in terms of many forms of beads, nails, plates, and spacers.

Autograft, theoretically, provides a superior delivery system. However, there are no large-scale clinical series and the optimal dosage is not known. Therefore, this mechanism cannot be recommended.

Allograft avoids the morbidity of harvest but may add the potential for infection serving as a sequestrum. The allograph can be modified to improve release characteristics. However, insufficient information regarding dosage, carrier and antibiotic choice precludes its routine use.

Calcium sulfate and calcium phosphate are biodegradable ceramics available as delivery mechanisms. Calcium sulfate is widely used when combined with vancomycin and gentamicin and provides high MICs up to 3 to 4 weeks. It does have superior elution profile compared to cement. Calcium sulfate can be injected into defects and fills the medullary canal as an adjunctive dead space. Management delivers high concentration of antibiotics with long elution times and degradates by chemical disillusion, which is relatively rapid.

Calcium phosphates are porous ceramics with variable porosity and because they integrate via a cell-mediated response, have longer incorporation times. Cerament is an antibiotic phosphate which is now part of an FDA study.

Bioactive glass is a synthetic silicate material that has cancellous bone-like three-dimensional architecture. As it undergoes degradation, it causes a local increase in pH with a direct antibacterial effect. When combined with antibiotics, it has been shown to kill planktonic and biofilm bacteria. It osseointegrates by the conversion of its surface layer to a hydroxyapatite layer similar to bone for rapid incorporation.

Cytosine is a sugar type polymer that can be modulated for specific drug elution in

biodegradation characteristics. We looked at this in a preclinical study a few years ago and found that reduced bacteria loads in contaminated wounds are present, with the majority of the sponge dissolved by 48 hours. It currently now is combined with other materials for wound healing purposes.

Hydrogel can be designed to encapsulate antibiotics that are released by external environmental factors such as a change in wound pH or vascularity. They can deliver antibiotics and be completely degradated within 48 hours, as well as deliver very high local antibiotic concentrations. A recent multicenter study compared hydrogel-coated plate to standard plates and revealed a significant reduction in infection rates for coated plates compared to uncoated implants.

PLA polymers have been used for years for biodegradable implants. Isomers have been modified to provide a material that can provide a local release of antibiotics and at the same time, stimulate osseointegration. Another advantage is that it can be mixed with other biodegradable materials or manufactured as nanostructures for additional biologic activity. These materials are biocompatible and can degradate to avoid the need for device removal.

This is an EM of a PLA nanofiber with and without vancomycin coatings suitable for use in coating implants. Numerous recent studies outside the United States document superiority of antibiotic-coated nails with the PLA coatings in terms of reducing infection compared to standard nails.

There are many other non-eluting implant coatings which are currently in development, such as silver, quaternary ammonium, polymers, and povidone iodine coatings.

In summary, direct local application of antibiotics works. Ceramics are currently the best alternative drug delivery mechanism. However, these other technologies are coming

on fast. Implant coatings are on the near horizon, as well. Thank you very much.

DR. BERTRAM: Thank you, Dr. Watson and presenters from Session 3.

And now we'll go to the presenter discussion. The moderators will be Dr. Paul Tornetta and Dr. Tracy Watson.

Dr. Paul Tornetta received his bachelor's degree in chemistry and mathematics from Franklin and Marshall College in Lancaster, PA. He earned his medical degree from SUNY Health Science Center at Brooklyn, New York, where he also completed his internship and residency in orthopedic surgery, followed by a fellowship in acetabular/pelvic fractures at the Hospital of the Good Samaritan in Los Angeles under Joel Matta. He is currently the Professor and Chairman and Residency Program Director in the Department of Orthopaedic Surgery at Boston University School of Medicine, and the Director of Orthopaedic Trauma for Boston Medical Center.

As previously introduced, Dr. Watson is currently Professor of Orthopaedic Surgery and the chief of the Orthopaedic Trauma Service at St. Louis University School of Medicine.

Dr. Tornetta, Dr. Watson, it's all yours.

DR. TORNETTA: Dr. Bertram, thanks very much. And thanks to everybody viewing today.

The panel gave a really nice discussion around a number of different comments and sections. I thought one of the things that stood out to me, and we do have a few questions from the audience we'll get to, but in speaking about this in advance, Tracy and I both felt that it warranted some discussion around how difficult it is to treat the problem when it occurs and how much effort we should be placing on prophylaxis, the concepts of combined products as brought up by the FDA people at the beginning of this session.

Mike, you've addressed that a little bit with the bioburden -- I mean with the vanco study. How do you feel about the differences in prophylaxis versus treatment?

DR. BOSSE: I mean, I think the key is prophylaxis, I think we need to prevent the infection. It's probably going to be much cheaper than identifying the -- in the open fractures, the 25% that get infected and then dealing with the late infections in that large cohort. So prevention, I think, is the key.

DR. TORNETTA: I agree. And to that end, I think that there's always some discussion with combined implants around the concepts of colonization versus infection. And Dave, you're sort of a biofilm expert and I think you know as much about this as anyone. Would you consider that decreasing colonization of an implant, for instance, in an open fracture model, would therefore lead to less aggressive and less infections in the long term? You're muted.

DR. LOWENBERG: Absolutely. We've even found in the lab that biofilms develop at a varying rate and also, interestingly, the sessile phase of growth of these biofilms starts developing really early and it's incomplete. It's not an on/off process, it's a very slowly evolving process, so anything to slow it down would be really very positive with a lower bioburden.

DR. TORNETTA: So for the panel, including Tracy, would it be reasonable -- because one of the things we're trying to accomplish was this workshop and again, I really credit the FDA with looking for solutions rather than just problems -- is how we define success. And I've always thought, and I'd like all of your opinions, that if we can reduce bioburden, that would be a very strong surrogate for reduction of infection. Like, would that be a reasonable efficacy marker if you were trying to get something to market, a new implant, a new technology. And I'll start with Dave since you're on mike and then maybe Mike and Tracy can chime in.

DR. LOWENBERG: I think that would probably be one of the best bangs for your buck you can get for acute trauma and acute injuries. I would think that would be a primary

place to focus.

DR. WATSON: I agree, I think historically it's been biocompatibility studies and so forth, looking at the elution of all of these adjuvants and of course, we have nothing because of the rigorous approval process. So I think efficacy at a local level on reducing bioburden is a much simpler and a much easier way to assess rather than biocompatibility throughout the entire body. So yeah, I totally agree with you.

DR. TORNETTA: Mike.

DR. BOSSE: Yeah, I think for looking at the high-end fractures, if we're closing the wounds that have a 30% recovery rate or bioburden, and the bioburden is atypical and not responsive to the antibiotics we're providing, we're basically set up for failure. So I think we really have to go back and look at the entire process and reinvent it.

DR. WATSON: You know, I have a question for both Mike and Dave. And Mike, you really hit the nail on the head where, for the open fracture, the data you showed, we basically know what the organisms are and the bioburden and you also demonstrated, as Dave alluded to, that a lot of the antibiotics are just not even effective. So most orthopedic traumatologists are creatures of habit. Why do we insist on getting cultures, then, because it looks like it's not really making a difference, it's just added cost? Is there any value, based on what you guys have just said, to continuing with cultures or how do you use them with fractures?

DR. BOSSE: Actually, I think that when we looked at the results, most surgeons did not get cultures. So I think your center may be different, but most guys just throw their hands up in the air and think that cultures are worthless and they treat with the skip protocols, which is 24 hours of a cephalosporin at the time of coverage and then basically, that gives you essentially no treatment and no coverage in the current climate. So that's what we have to address.

DR. WATSON: Yeah.

DR. TORNETTA: There's some questions coming through the panel, so I'll just go through those, so a couple looking really at bioburden and the initial phase. So other than antibiotics, what options are there to address the biofilm perioperatively? And then a further question that really gets into the same issue of how is CDER and CBER working to get these combination products together. And Dave, why don't we start with you about things that you're seeing coming forward to reduce bioburden. I mean to reduce the biofilm and treat it.

DR. LOWENBERG: Sure. First of all, once a biofilm forms, there's currently nothing out there that will eliminate it other than surgically removing it. There have been proteins, enzymes really, isolated in nature, that are very effective at eliminating biofilms. However, they're so immunogenic they've never gotten through the laboratory stage to get into human use and I doubt they will. Jay Parvizi mentioned earlier today, and I think he's right, phage therapy. We're doing some stuff on that with biofilms now, we have a grant and I think there's a future to that.

But at this point in time, maybe some other novel ideas might exists, one being we can't really beat bacteria every time, in all likelihood, and to communicate with them, which some labs around the world have done to short-chain RNA, to put them in a permanently dormant state, might be another reasonable option for treatment. Clearly the widespread use of antibiotics is failing.

DR. WATSON: I have a question for everybody on the panel. And, Mike, you alluded to host factors, but also how to close a wound and knowing the overall biologic health of a wound is probably the biggest preventative measure that we can take. So is anyone looking at the wound itself, in other words, markers such as the neovascularization or metabolic factors in a wound, to determine, as per your point, when is it best to close a wound?

Because I think we're kind of looking at the end result and not the beginning, we're not looking at the wound itself, we're looking at the colonization and the infection. We need to kind of backtrack and look more at the biology of the wound itself. So how do you think we need to get there?

DR. BOSSE: Well, I mean, I think it's a great point. The Department of Defense had some research where they looked at -- I think it was serum calcitonin in the fluid from the wound bags and showed that that correlated with the successful wound closure and later infection rates. There certainly should be some biomarkers we could identify to make the markers of the optimal time for wound coverage. Probably once a wound is cleaned, the early the coverage the better because we'll knock down at least the nosocomial contamination.

DR. LOWENBERG: Tracy, in that regard, also, you were the first person to publish a great study on that to show that it doesn't matter what the bacteria is in a wound, you have to create a living wound and your study was probably the landmark study on that. In fact, we adopted that for a different reason, for all our chronic infections, our chronic osteos. We don't even care what the organism is. We want to know if it's prokaryote or a fungal in a eukaryote and we have an algorithm from there and it didn't change the outcome whatsoever. It's creating a living wound healthy environment. That is what truly matters.

DR. WATSON: Right, right. Have you guys looked at, Dave, any quorum sensing modification to -- as you've mentioned, the Pavlovian theory of bacteria that prevent the bacteria from morphing to this sessile state through their own intercommunication mechanisms?

DR. LOWENBERG: That's really where we want to go in the future. We just started on some signaling -- well, very basic stuff of looking for indictors of inflammation and how that changes things. But the real nuts and bolts of this is going to be with short-chain

molecules to communicate back and forth with the bacteria. And there are some places around the world that have done that very preliminarily, but I think that's the future and that's where I think resources should be pushed.

DR. WATSON: Yeah, yeah. Exactly.

DR. TORNETTA: There was a question for you, Mike, just on the -- I think you saw it in the chat, just how are you dealing with the heterogeneity of injuries in these open fracture trials?

DR. BOSSE: Yeah, that's a great point and doing research on high-end fracture patients is challenging because of the injury in the patient. And I think that, one, you need a good funding source because you need a lot of patients, so you need to select a fracture that has a fairly high complication event rate so your *n* can be lower and then you have to focus the inclusion criteria and really specify the injury, a host, and environmental characteristics that you want to use in your analysis and capture those so that you can control the populations of the *n*. It's doable, but it's difficult.

DR. TORNETTA: And then I had one other question and I think everybody -- for everybody on the panel to answer. You know, when we look at scientific rigor, we set these exceedingly arbitrary numbers that mean something, like a *p* of less than 0.05, right, which is -- it's arbitrary and things in dichotomous outcomes are even more fragile where a couple of infections or non-infections in a relatively rare event can swing the relative risk reduction by half.

When we start to look at these larger studies that hopefully will get done, but let's just say that we work with the FDA and a wonderful combination product is figured out by somebody and we try to get that released, what would you use as a threshold to be able to reduce that -- release that to other surgeons? So we have to assume there are safety issues and efficacy issues, and I would choose to separate those and say what is the safety

threshold and what is the efficacy threshold that's required, or should be required in principle, to release something that has real potential to decrease infection?

DR. WATSON: I think the safety and efficacy should be based on a predicate device such as antibiotic cement, not to have any more toxicity than what is currently seen with all the talks we just heard on antibiotic spacers, right? So I think that's kind of the only gold standard we have right now other than the topical application, which there's pretty good data on that. So I think we don't need to exceed that, we just need to make sure it doesn't go over that threshold.

In terms of effectiveness, we have a really good model. I mean, Mike's data showed 30% of open fractures get infected. So I think it's a fairly low bar if we can come in underneath that in some respectable fashion that I think we've done a nice job. So I think the onus is pretty low right now and anything that beats what we currently have should be approved.

DR. TORNETTA: And what about for problems that are not an open fracture with a 30% infection rate in a worst-case scenario, what about injuries like condylar tibial plateaus that systemically has a 6% infection rate? You know, what do we need to drop it to? Is anything a good thing? Do you need 50%?

DR. WATSON: No, I think anything is a good thing. I mean one infection, you know, who cares, you're just eating up a massive amount of hospital, so any reduction is better than what we have now, which is no reduction, right? So I think the bar should be fairly low because we're talking extremely debilitating and cost -- you know, it just eats up the money. A fracture infection is a disaster for everybody involved, so anything's better than what we currently have. An improvement of 1% is still -- that's a pretty big number.

DR. TORNETTA: Mike or Dave? Mike, you're muted.

DR. BOSSE: I think improvement is important, as Tracy alluded to, but I think that for

the small numbers like that, say, for infections of closed fractures, you know, to expose everybody to a new technology or therapy and new cost, I think at the end we're going to have to do a cost balance, you know, what is the cost of treating three infections versus the cost to reduce one infection?

DR. WATSON: Well, I think you could -- as you alluded to, there's the high-risk fractures, high-risk closed fractures such as pilons and plateaus, which those are kind of an outlier. Routine tibia and femoral fractures probably -- you know, I agree, that's probably a waste of money because their infection rate is fairly low assuming you know what you're doing.

DR. LOWENBERG: I would say there's another area of improvement that we could get just global, I mean across the board. I think our education in the treatment of infections and prevention, as well as proper debridement is not that highly regarded among many residencies and training programs and I think we, as a group, might be able to do a better job on stressing these things and the problems before us. And infection has always been seen as the unglamorous thing sent to academic medical centers and county hospitals because no one wants to treat it and maybe this culture needs to change, too.

DR. TORNETTA: All right. Well, I want to thank the panel, I think we're just about on time, so I'll hand it back over to Dr. Bertram.

DR. BERTRAM: Thank you, all. Well, I hate to say this, we have one session left. So Session 3, again, greatly appreciated. Thank you for the stimulating discussion and perspectives. With that, let's take a 5-minute break and see you in a few.

(Off the record at 10:53 a.m.)

(On the record at 11:00 a.m.)

DR. BERTRAM: Welcome back, everyone, to our fourth and final session entitled "Advance Development of Needed Orthopedic Device Technologies: (Physician Community,

Device Manufacturers, Academia, Governmental Agencies, Regulators and Patients)."

So with great pleasure I get to introduce a colleague of mine, Dr. Larry Coyne. Dr. Coyne serves as the Division Director of the Division of Restorative, Repair and Trauma Devices in the Office of Orthopedic Devices (OHT 6). Prior to his current position, Dr. Coyne's 30-year career in FDA has also included serving as an Assistant Director in OHT 6, a Branch Chief in the Office of Device Evaluation, a first-line supervisor and Director of the Engineering Branch at the Winchester Engineering and Analytical Center, an FDA field laboratory, and a materials research engineer in CDRH's Office of Scientific Technology, now known as the Office of Science and Engineering Laboratories. Dr. Coyne has a doctoral degree in polymer science and engineering from the University of Massachusetts at Amherst and a bachelor's degree in chemical engineering at Tufts University. The title of his presentation is "FDA Perspective: Emerging Concepts Related to Orthopedic Device Technologies."

DR. COYNE: Good afternoon. I'm Dr. Larry Coyne, Director of the Division of Restorative, Repair and Trauma Devices in the Office of Orthopedic Devices in CDRH.

As a disclaimer, the findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration, are the views of the author, and should not be construed to represent any Agency determination or policy, and any mention of commercial products is not to be construed as either an actual or implied endorsement by the Department of Health and Human Services.

My presentation will include a brief summary of the elements of FDA's least burdensome provisions, benefit-risk factors to be considered in CDRH premarket review decisions for various submission types, and uncertainty factors in benefit-risk assessments specifically for de novo classifications, PMAs, and HDEs.

As stated in Agency issued guidance, guiding principles for applying the least

burdensome provisions include requesting the minimum information necessary and using the most efficient means to resolve regulatory questions and issues. The least burdensome principles are to be applied to reviews of PMAs, de novo classifications, and HDEs. For submissions for combination products, the least burdensome principles apply to the device constituent of a combination product.

In addition, the guidance states that while a randomized controlled trial constitutes one form of valid scientific evidence, there are alternatives that may constitute a more efficient means for addressing clinical issues, including the use of historical controls and alternative sources of data including registries, claims data, and published literature.

From the standpoint of benefit-risk factors to be considered in substantial equivalence assessments for devices reviewed under the 510(k) pathway, FDA guidance recommends consideration of the extent of the probable benefits and probable risks and the degree of uncertainty in their assessments, as well as other factors including patient tolerance for any risks in light of probable benefits, risk mitigation achievable through labeling, and the potential reliance on postmarket data.

For benefit-risk assessments for PMAs and de novo classifications, FDA recommends similar factors be considered including again the extent of the probable benefits and risks of the device, as well as the degree of uncertainty in their assessments. Considerations include patient perspectives on the relative benefits and risks of the device, risk mitigation facilitated through labeling, the potential reliance on postmarket data, and the availability of alternative treatments.

FDA has also issued guidance regarding uncertainty factors to be considered in benefit-risk assessments for devices reviewed under PMAs, de novo classifications, and HDEs. The extents of the probable benefits and risks of the device and the degree of uncertainty in these assessments should be considered in conjunction with those of

alternative treatments or standard of care. Patient perspectives, the extent of the public health need, the feasibility of generating sufficient clinical evidence pre- or postmarket, and the likely effectiveness of utilizing labeling and other available tools to mitigate risks should all be considered.

Other points for consideration in FDA's determination of reasonable assurance of the safety and effectiveness of a device are as follows: The evidence FDA requires for PMAs, de novo classifications, and HDEs has been flexible and is tailored to the device. The evidence to support this determination may well vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, as well as other factors. Compared to a PMA or a de novo request, both of which require a demonstration of reasonable assurance of safety and effectiveness, there is generally likely to be greater uncertainty regarding the benefit-risk profile, based on the evidence submitted, in an HDE application. This is an acknowledgment of the challenges in generating sufficient clinical evidence to demonstrate a reasonable assurance of effectiveness when the patient population is very small. Hence, HDEs are not required to demonstrate reasonable assurance of effectiveness.

There is generally more flexibility in the amount of clinical evidence needed for devices than for drugs and biological products because they are subject to different statutory criteria. The mechanism of action and modes of failure are generally more predictable and better understood for devices than for drugs and biological products. The design process for a device is more often an iterative process based largely on rational design and nonclinical testing rather than clinical studies.

In summary, FDA considers the totality of evidence regarding the extent of probable benefits and the extent of probable risks of a device, including the extent of uncertainty in the benefit-risk information. FDA also considers the appropriateness of risk mitigations and

the collection of postmarket data to address the uncertainty in the benefit-risk information. Such benefit-risk and uncertainty considerations are applicable to premarket submissions for devices incorporating infection control technologies.

This concludes my presentation. Thank you very much for your attention.

DR. BERTRAM: Thank you, Dr. Coyne.

Our next presenter is Dr. Richard Iorio. Dr. Iorio is the Chief of Adult Reconstruction and Total Joint Arthroplasty Service and the Vice Chairman of Clinical Effectiveness at Brigham and Women's Hospital. He is the Richard D. Scott Distinguished Chair in Orthopaedic Surgery. He co-founded Labrador Healthcare Consulting Services, Responsive Risk Solutions, and the Value Based Healthcare Consortium in 2015. Dr. Iorio is a national expert in hip and knee replacement, patient optimization, and the treatment of osteonecrosis, physician and hospital quality and safety and a leader in the implementation of alternate payment paradigms and quality and safety initiatives in orthopedic surgery. He is the president elect for the American Association of Hip and Knee Surgeons. The title of his presentation is "Developing Protocols and Guidelines to Minimize Infection Related to Orthopedic Devices".

DR. IORIO: Hi, my name is Richard Iorio. I'm the chief of adult reconstruction and total joint replacement at Brigham and Women's Hospital in Boston. I'm here today to speak about developing protocols and guidelines to minimize infection of orthopedic devices.

I don't have anything to disclose regarding this talk.

There are four possible intervention types to modify infection risk. We've got antibiotic stewardship and customization to local biomes with alternative delivery mechanisms. We have perioperative and intraoperative interventions such as MRSA screening and all the accompanying interventions to prevent MRSA proliferation. We have

antibiotic delivery in the implant or bacterial resistant implants, which is a hot topic as of now but not currently used that often. And we have patient optimization risk factor improvement, which has been an area of focus for the past few years.

In 2012 when I went to NYU, we entered into value-based payment paradigms and using care management and physician utilization modification. We were able to decrease length of stay, decreased discharged inpatient facilities, decrease the cost of the episode of care, but we had not significantly altered readmission rates and infection rates to my satisfaction.

We then looked at our patient population and realized we had some high-risk patients with multiple comorbidities including morbid obesity, uncontrolled diabetes, and poor nutrition; smokers, neurocognitive, and dependency issue patients such as alcohol and narcotics abuse; high-risk VTED patients that required aggressive anticoagulation; fragility patients who had poor physical deconditioning and fall risks. We did not have any infection prevention protocols in place at that time, and we had a number of patients with cardiovascular and stroke risks.

Looking at that patient population, we then implemented programs to help control those high-risk populations. One of the protocols we use for infection prevention was the vancomycin and dilute iodine prevention protocol where we did dilute povidone-iodine lavage prior to closure in all high-risk patients, and then added vancomycin powder above and below the fascia. These high-risk patients are listed here and encompassed many of the high-risk variables we found in our bundled payment high-risk population.

We found that our high-risk patient population infection rate went down 20% with the implementation of this protocol, and we then instituted this in our patient population. This was not a statistically significant sample as it was small numbers, but we have obtained funding to implement this study nationally in multiple centers and we'll see if this is

generally able to be scaled to a larger population.

We took the high-risk patient variables, placed them in a grid to predict infection and readmission risk, and we call this a perioperative orthopedic surgical home. We used this outline for high-risk patients to decide who needed to be optimized and have surgery delayed. We looked at nomograms that predicted the infection and readmission risk of these patients. Patients with three or more risk factors were at high rates of readmission and infection and were then subject to this modification program.

Here's a number of the programs that we implemented, including MRSA screening and smoking cessation, weight control, drug and alcohol interventions, and other health improvement mechanisms in order to show a better health status in these patients and better outcomes.

As you can see here, we reduced our 90-day readmission rates from 13% to less than 5%. And this is in a Medicare population where the general 90-day readmission rates are around 18%.

The perioperative orthopedic surgical home showed us that we could modify remission rates and infection by delaying surgery, but could we improve those rates if we implemented the modification programs and then those patients reentered the system and had surgery? Could we improve their projected quality metrics?

We looked at a large population of patients in our bundled payment program, and we compared those results to see if we were able to improve their ultimate outcomes. We were able to decrease length of stay. We were able to decrease discharge to post-acute facilities. We were able to decrease the cost of care and the readmission rates of the patients who underwent the optimization guidelines.

Here is that data presented in a graphic format and you can see that the results were statistically significant. We also were able to show financial significance in decreasing the

cost of their care by having them go through the program.

So our conclusion was that the identification and medical optimization of comorbidities prior to surgical intervention may enhance the value of care joint replacement candidates received. And using a standardized multidisciplinary approach to the medical optimization of these high-risk patients may improve patient engagement and perioperative outcomes while reducing the cost associated with joint replacement.

So alignment of the physicians involving the patients in the shared decision-making about when the risk of surgery becomes appropriate, and then optimizing their medical status to match that risk tolerance is important. At NYU and at the Brigham, we've hired a risk stratification coordinator to manage these poorly optimized patients and to coordinate their referral to the optimization programs. And in today's quality driven environment, it's no longer economically feasible to simply accept increased risk of poorly managed patients. The surgeons need to get involved in making sure that these patients are getting optimized prior to surgery.

At the Brigham, we implemented this program between 2018 and 2019. We decreased our surgical site infection rates with total knee replacement to 0.58%, and for total hip to 0.79%. Our quality metrics all improved, our length of stay decreased, and our surgeon satisfaction was greatly improved as their volume efficiency quality metrics and finances were enhanced.

At an academic medical center, you have four possible options to implement these programs. It could be surgeon-directed, but that really isn't programmatic enough to affect change. That was what we did the first couple of years at NYU. A preoperative clearance center or anesthesia can implement a POSH program. PCPs in general internal medicine doctors could. We've opted for an orthopedic surgery directed referral center with an optimization core coordinator who was a PA. That PA is able to see patients referred to him

or her from the division or outside of the division and make referrals to other subspecialists and intervention programs, and the program was designed to be revenue neutral.

This is a depiction of all of the subspecialists we have on board, and to whom we can refer patients to help us get our patients improved prior to surgery.

Here are some other subspecialists, as well.

So our PA coordinator is able to serve as a resource for all of our patients and surgeons, and she can coordinate referrals and follow patients until they meet the criteria for surgery and then send them back to the referring attending. If patients aren't able to modify their risk factors, then another appointment is made with the surgeon and a frank discussion is had about risk, whether or not the patient is able to get to an optimal baseline or not. Our PA coordinator also works with our preoperative clearance center to make sure patients are optimized.

In conclusion, these optimization programs can be extended to any elective orthopedic spine, sports program, or surgery procedure. And smaller institutions may be able to combine programs for surgical subspecialties. In the ideal state, patients should be referred to those optimization programs prior to coming to the orthopedic specialist with joint replacement. Internal medicine, family practice, rheumatology, and GIM physicians should be thinking about optimization prior to referring the patients to the orthopedic joint surgeon. Thank you.

DR. BERTRAM: Thank you, Dr. Iorio.

Our next presenter is Dr. Joseph Wenke. Dr. Wenke received his bachelor of science from Baylor University in 1997 and a Ph.D. from Texas A&M University in 2003. Dr. Wenke arrived at the U.S. Army Institute of Surgical Research in San Antonio, Texas as a National Research Council postdoctoral fellow in 2003. The following year, he accepted a position as a research physiologist and has been the chief of the orthopedic trauma since 2007. His

primary research focus has been to improve outcomes of open fractures, which are fraught with complications such as infection and nonunion.

Before kicking it into his presentation, just a reminder, please, everyone, submit your questions for panel discussion at the end.

The title of Dr. Wenke's presentation is "Scientist's Perspective: Translating a Technology from Bench to Bedside."

DR. WENKE: Greetings. I'd like to thank the organizers for the invitation to speak. The topic is Scientist's Perspective: Translating a Technology from Bench to Bedside. This is a very important and timely topic for this workshop. And my name is Josh Wenke, I'm at the Institute of Surgical Research in San Antonio.

So my disclaimer basically states that this is my ideas, not the Army's, and I have no financial relationships to disclose.

So the issue. Millions of ideas, thousands of funded projects, probably few to hundreds of new products each year, many through a 510(k), which really aren't going to make a big splash. It's not going to change practice, kind of a "me, too" type technology, "me, too" product. And then there's few truly new products, things that had to go through the entire PMA, the IND or IDE, true new devices or drugs. And even fewer of those, I'd probably even argue, next to zero new products that come in that actually make an impact.

Why is this happening? Well, most people state it's because of this Valley of Death. This kind of cartoon or graph shows on the Y-axis the resources or dollars spent on each one of these subtasks. Discovery is on the far left and what that shows or demonstrates is the amount of dollars for innovation for science. This would be traditional NIH grants in funding sources like NSF. On the far right you would see the commercialization dollars, often Phase II, Phase III clinical trials. As you can see, there's large amounts of money for both of these. It's in the middle. The hardening studies, the applied studies, the safety

studies, the GMP, the GOP, there's not much funding for them. This has been widely accepted and thought of for now decades.

The following slide shows other depictions of people's cartoons that kind of try to explain this. The one thing they all have in common is that a lot of technologies, lots of good ideas, die between initial discovery and never even get into clinical trial.

The bottom left actually shows that there's two Valley of Deaths. There's a second death after the commercialization and FDA approval where just not enough sales are made and the product just kind of dies after approval and never really makes an impact. We're just going to talk about kind of this first part because it's from a scientist's perspective and the short amount of time. We're going to talk about some of the impediments and suggestions that could help get technologies and ideas from bench to bedside.

First, we're going to talk about the products or the actual technology itself. I think a lot of times the therapeutic or the technology really isn't aligned with the current treatment paradigm. This is because the scientists and the innovators really don't understand what is going on clinically, how the patient is treated, how wounds are treated, and the proposed solution doesn't really fit the problem.

The next thing is the product needs to be not overly complicated. You can't sit there and have to read 30 minutes of instructions and directions in the operating room or in the clinic. That's just not going to work.

The next thing is it cannot add appreciably more time. Things that take 30-minute procedures into an hour, things like that will just not ever be picked up and taken out.

It can't have prohibitive upfront costs. This means a couple things. First, it cannot require a lot of capital by hospitals or when it rolls out. But probably more important than that is that the pathway cannot cost a lot more money. I was part of a project that actually has developed a new biomaterial and this biomaterial was performing perfectly well, it was

licensed by a company. But whenever they wanted to go in to start doing safety tests, they found that it was going to be over a million dollars of just GMP upfront costs because there's no records, no files for this new material, and it simply just did not make sense for the company. So that million dollar price tag, before you get into the GOP safety studies and the ISO testing, was just too much. That's the prohibitive upfront cost I'm talking about.

And then finally, the technology or the product must have meaningful effect size. What I mean by this is a lot of scientists get really excited about significant difference. There's a big difference, a large difference between significant and substantial.

The next impediment or suggestions, really, is focusing on the scientist. First and foremost, scientists speak a different language than clinicians and businesses. There is a lot of training on what is innovation and all the rules and all the standards that they're going to be held to, to get funding, to get a tenure track position, and to get tenure and then promotion and most of that, the vast majority never really touches on getting a product to market.

One of the things that the scientist can do is use relevant animal models. What I mean by that are animal models that when you first are starting to assess things, whether it will work or not, that would be predictive of actual clinical success.

Next, it needs to be a stringent model, something that where everything you try doesn't work. We want things that actually have a standard and things fail. It's a way we can separate good from great.

We need appropriate clinical controls. These clinical controls not only allow you to ensure that it's a stringent model, but it gives the surgeons, the clinicians, some enthusiasm about it. And more importantly, it allows businesses to actually judge things and whether or not they want to invest. The little bit of the experience I've had with companies, I've

seen them actually do studies where they would take a model that they trust and do two groups into three and then decide whether or not they're going to license that technology.

The next thing we're going to focus on is the system. This might be a more difficult thing to focus, but I think probably has the most impact. First, the system. You know, the grants fund innovation, not products. It's about discovery and innovation. And that's why on the graph on that far left side, you see the discovery aspect and this is a big problem. There's not funding, and a suggestion would be to have more funding for these hardening applied studies, these ISO testings, the GOP, the GMP. These are things that if we can de-risk the company buy-in, that would have profound impact.

The following is you really have to make sure once you get the technology and you get the patent application out there, that the right company licenses the technology. There have been times where a device company licensed something that ended up being a drug and they did not know what to do with it. Other times, a large drug company got something that was kind of a tweener, but it was a drug, but they looked down and this billion-dollar company said, "Well, we don't want to push something that might only have a revenue of 50 million or a hundred million dollars a year." So it's really important to him to match the technology or the future product with the right company.

And finally, the summary. These are some things I think we need to do to translate promising bench discoveries to bedsides. PhDs and MDs need to talk. Anytime you scientists can interact with MDs and go to M&Ms and different meetings and really understand the problem, this just really doesn't happen very often. I think we need to educate scientists what is desirable to companies. Instead of just always picking the most innovative new drug or device, actually start including some of the things that have a record with the FDA, which will lessen the upfront cost to get it approved.

I think we need, number three, a better understanding by all of the FDA approval

process and what is required. I think this has been black-boxed to a lot of both scientists and clinicians.

And then finally, and probably the things that have the most impact, is bridge funding for applied studies, the GMP, GOP, and the safety and feasibility of studies; again, de-risking the companies. The DoD is trying to do this. I know NIH does this with a lot of their STTRs and SBIRs. These are a great step, but I think we need to figure out how to do more and this probably would have the most impact in this realm.

Finally, I'd like to thank you for your attention. And if we don't have an avenue to ask and answer questions here, my email is on the first page. Thank you.

DR. BERTRAM: Thank you, Dr. Wenke. I have to say, your slide on the Valley of Death brings back personal memories from my own graduate experiences when I was getting my Ph.D. So thank you.

Our next presenter shouldn't be a stranger to anyone, particularly given an earlier presentation in Session 1. For those unable to attend the earlier session, Dr. Javad Parvizi is a board certified orthopedic surgeon and has been at the Rothman Institute since 2003. He specializes in the management of young patients with hip disorders. He completed his medical school education in the United Kingdom and has served as the president of Musculoskeletal Infection Society as well as the Eastern Orthopedic Association. The title of his presentation is "Clinician's Perspective – Joint Arthroplasty Devices: Analysis of Clinical Worth and Advances of a Technology to the Market."

DR. PARVIZI: Good morning, my name is Javad Parvizi. I'm a Professor of Orthopedic Surgery at Thomas Jefferson University. And once again, I'm grateful to FDA for providing the podium to discuss this particular topic. I will be providing the clinician's perspective on how to improve clinical worth of an anti-infective technology and advance the technology into market. Next slide.

My disclosures is to remain the same -- next slide -- and unchanged from the first talk. Next slide.

We all know that total joint arthroplasty is a very successful elective procedure that restores function to patients and alleviates their pain. Next slide.

Because of its success, it continues to be utilized on a much larger scale and by one projection, we might be doing about three million joint replacements in the United States by the year 2030. Next slide.

Infection after joint placement, however, is not a simple problem. It's a devastating complication that can happen in about 1% of the time. Next slide.

It leads to implant failure, mortality, reduced quality of life, and places huge economic burden on the healthcare and the society. Next slide.

So to prove the clinical benefit or worth of an anti-infective technology, we first need to have a definition. Using the FDA's definition, a clinical benefit is defined as any positive therapeutic effect that's clinically meaningful in the context of a given disease. Next slide.

Anti-infective technologies can fall under two categories, preventative or therapeutic. For preventative, the primary endpoint would be a reduction in the incidence of infection and for that, we need to have a definition for infection, which was fortunately provided by the International Consensus Meeting in 2018. And for therapeutic, we need to define success, and Musculoskeletal Infection Society provided that particular definition for success recently. Next slide.

The issue is when you have a condition with 1% incidence, to be able to prove clinical worth you need a huge number of patients, and these clinical trials become almost prohibitive to perform to reach the statistical power that one expects. Next slide.

So let's assume an infection rate to 1%, a statistical power at 80%. In a 1:1

superiority trial with an attrition of 10%, we would need over 11,000 patients to prove the clinical worth or efficacy of an anti-infective technology. Next slide.

We all know this is prohibitive. No academic center is able to perform this on their own. This would need to be a multicenter study spanning over multiple years. And industry partners may have little appetite in sponsoring this type of a study because it would take years to do at a huge cost to them and the return on their investment may not be justified. Next slide.

So what do we need to do? One of the options available to us is to concentrate on a condition such as irrigation and debridement that has a very high failure rate, 50%. Even one- to two-stage exchange arthroplasty has a recurrence rate of 20%. So target and study the anti-infective benefits of these technologies in conditions such as these that have a much higher failure rate. Next slide.

So in a situation like this, perhaps a patient population about 4 to 500 would suffice to show the worth of the anti-infective technology. But even this would require quite a multicenter setup and would most likely take at least a year or two to complete. Next slide.

It's important to know that, though, some of these clinical trials conducted in one region or a country may not be applicable to other regions around the world. For example, the incidence of resistant organisms from a country to another varies, as is seen on this slide. Next.

So the other process would be for the FDA or other agencies to consider an accelerated approval process -- next slide -- quite like what's done with some of these drugs for critical life-threatening conditions. After all, the incidence of PJI and the success of treatment has remained fairly constant over the years and we have not been able to make much of a dent. So many of us would argue that management of orthopedic infections is one of those clinically unmet areas. Next slide.

There is another possibility, we could use surrogate endpoints as opposed to seeing a reduction in infection rate or efficacy in treatment. These could include physical signs and resolution of infection, laboratory findings, serological markers, for example, or radiographic parameters. Next slide.

We could also target the first 2 years after a procedure as incidence of infection appears to be much higher in the first 2 years as opposed to throughout the life of the prosthesis. Next slide.

So if you were to combine the clinical findings together with, let's say, the serological markers, it's possible that we could have up to about 90% sensitivity in determining whether an infection event has or has not been resolved. Next slide.

The other possibility would be for the Agency to clear the anti-infective technology for one particular application or indication, but then have a broader application later. This happened with Pfizer, and I was part of a team that came to talk to VRBPAC and Pfizer was arguing at the point that their clinical and pivotal trial on the tetravalent vaccine for *Staph aureus* -- next slide -- that was being conducted in the spine field could be applicable to total joints and for that matter, all other orthopedic applications. Next slide.

Because the pathophysiology of infection, especially related to *Staph aureus*, is the same, its similar accessibility, immune responses elicited by the vaccine and similar risk factors for SSI. Next slide.

The other alternative is for us to conduct these studies in high-risk groups, patients that have a much higher instance of infection than the general population. Next slide.

Patients with diabetes, obesity, or other types of conditions that puts them at a higher risk for infection. Next slide.

Finally, the perspectives are very important. Next slide.

Are we looking at this clinical worth from patient's perspective, medical community

or industry's perspective? Next slide.

This needs to be taken into account by the FDA or the other agencies when they're developing their rationale for approval process, and also to the generalizability of these findings when the clinical trials are done. Next slide.

There is a difference between marketing and innovation, which we are all aware of. Next slide.

And not every innovation or product has helped our patients. And here's an example of so many that unfortunately ended up hurting our patients in the process. Next slide.

One thing is clear, that the current approval process happens to be extremely arduous and perhaps cost prohibitive for us to prove the clinical worth of many anti-infective technologies. And it is possible that many of these grapes will die on the vine and technologies will be stifled from reaching the patients and the medical community. Next slide.

Perhaps the time has come for the FDA and other agencies to look into these anti-infective technologies and clear them for medical use and for the benefit of our patients. Thank you very much.

DR. BERTRAM: Thank you, Dr. Parvizi.

Next up is Mr. Robert Durgin. He holds a law degree from the Tulane University School of Law and a bachelor's degree in government and Russian language from the University of Notre Dame. Mr. Durgin retired from the U.S. Marine Corps Reserve as a lieutenant colonel. He currently serves as the Worldwide Vice President, Regulatory Affairs for the Depuy Synthes Companies of Johnson & Johnson since June 2015, and has responsibility for providing strategic leadership for the regulatory affairs function of the world's largest orthopedic enterprise. The title of his presentation: "Joint Arthroplasty Devices-Industry Perspective: Orthopedic Device and Regulatory Challenges in the United

States."

MR. DURGIN: Good Morning. My name is Bob Durgin and I serve as the Worldwide Vice President of Regulatory Affairs for the DePuy Synthes Companies of Johnson & Johnson Medical Devices. Today I will be sharing some industry perspectives as a representative of the Orthopaedic Surgical Manufacturers Association.

Here is my disclaimer and disclosure.

Today I will touch on the following topics: unmet clinical need, the regulatory environment for anti-infective devices, the regulatory challenges regarding claims and clinical evidence expectations, and I'll conclude by respectfully suggesting that regulatory flexibility is needed in order to best serve patients in the United States.

Over the past 15 years I have had the opportunity to interact with the FDA on at least three projects involving implants with antibiotic coatings. As I reflect on those interactions, there have been two primary take-aways. First, that many orthopedic surgeons are passionate about finding a pathway to bringing these devices to American patients due to the poor outcomes, such as those depicted in these images and as you have heard from previous speakers. Second, manufacturers have been unable to meet the FDA's clinical evidence expectations for these types of devices. Thus, we have what I have been referring to as the regulatory riddle of orthopedics.

What is clear is that numerous orthopedic devices with anti-infective technologies have been registered by regulators outside of the United States. This is a non-exclusive list of such devices available to patients outside the United States who have had access to these technologies for more than a decade. The prevalence of these solutions makes it abundantly clear that a least burdensome regulatory strategy is attainable. We collectively owe it to American patients who are at risk of infection to find a solution to the U.S. regulatory hurdles.

There have been some regulatory successes for American patients. Antibiotic-loaded bone cements have been used clinically since the 1970s as prophylaxis in primary surgeries. The FDA has promulgated a rule classifying these devices as moderate-risk Class II devices which can be cleared under the 510(k) program. However, these clearances do carry significant labeling restrictions.

We have also seen a number of devices with antimicrobial coatings cleared through the 510(k) process, most of them non-orthopedic products. This slide depicts a non-exhaustive list. What is important to note about this list of devices is that the clinical claims have been limited to language such as "inhibit bacterial colonization on the pin or wire."

The flexibility that FDA has demonstrated in clearing these critically needed devices as early as the 1990s has been incredibly beneficial to American patients. In some cases, it has changed the standard of care. The most compelling example is the 2017 guideline published by the Centers for Disease Control and endorsed by the World Health Organization recommending the use of triclosan-coated sutures for the prevention of surgical site infections. These recommendations would not have been possible without FDA's flexibility in allowing the commercial availability of the product. The impact that coated sutures has had on the U.S. healthcare system and for general surgery has been profound. The orthopedic industry is seeking similar flexibility in how we can demonstrate the safety and effectiveness of our products.

It must be acknowledged that when the Agency is reviewing antibiotic-coated implants, it must make a challenging benefit-risk determination. Some of the benefits and risks a regulator must take into consideration are shown on this slide. The benefits include localized delivery of antibiotics resulting in a potential reduction of risk of postoperative infections; reduced systemic antibiotic exposure to address postoperative infection-related complications; and fewer revisits, reoperations, and serious outcomes such as amputation

and death. We would submit that the benefits and the risks are well understood and that the benefit-risk determination favors making orthopedic implants with antibiotic coatings available to American patients.

When solving this regulatory problem, the FDA has various tools at its disposal. The first pertains to the level of flexibility it exercises with respect to how the antibiotic coating is described. The second is the level of evidence the Agency requires to conclude that it has a reasonable assurance of the safety and effectiveness of the device. Of course, these are interrelated considerations. Recently, industry has been encouraged to make direct claims regarding a reduction of the risk of infection in humans. The impact of this encouragement is to increase the level of clinical evidence required to obtain a marketing authorization from the FDA.

As reflected on this slide, however, other claims language has been deemed acceptable and cleared by FDA in the past. For all three clearances, the cleared labeling was qualified by reference to non-human testing and, for the XenMatrix device, the effect was described as "inhibiting microbial colonization on the device." Most notably, 510(k) clearances which allowed statements of no correlation between preclinical testing and clinical outcomes is notable. The orthopedic industry would be thrilled to see the flexibility employed in the cardiac space.

Ten years ago, FDA cleared a pressure injectable peripherally inserted central catheter with the highlighted language. If a higher-risk cardiac device can be made available to American patients, it begs the question of why we have not been able to do so in orthopedics. It is exactly this type of regulatory flexibility that would go a long ways towards making anti-infective technologies available to American orthopedic patients.

The regulatory hurdle that has proved insurmountable for industry has been the Agency's expectations regarding the level of clinical evidence. It is worth noting that, by

regulation, the definition of valid scientific evidence includes not only well-controlled investigations and partially controlled studies, but studies and objective trials without matched controls, well-documented case histories by qualified experts, and reports of significant human experience with a marketed device. Simply put, the regulatory definition does not require the type of evidence at the top of the pyramid for FDA to conclude that there is a reasonable assurance of safety and effectiveness.

Given the difficulty and the economic reality regarding the conduct of a large-scale clinical study, industry respectfully suggests that the FDA exercise regulatory discretion to accept real-world evidence regarding anti-infective technologies.

This slide depicts a real-world example of what is possible from a regulatory perspective. The device in question has had a dramatically different regulatory experience in the United States and Europe. In Europe, the device has been CE marked since 2005 and has been recertified three times, including as recently as this year. In the United States, over that same time period, two separate marketing applications have been withdrawn as a result of the FDA's evidentiary expectations. The primary difference between the two regulatory reviews has been the level of clinical evidence required.

It is time for all concerned stakeholders to develop a clear strategy for how to address a clear unmet clinical need and to optimize patient outcomes. We need flexibility in two areas: claims language and the level of clinical evidence. Colonization claims have been deemed acceptable by the FDA in the past and we would ask that the Agency considering doing so again.

While FDA has expressed a willingness to be flexible on the level of clinical evidence, we have yet to find an acceptable level of real-world evidence to support these technologies. We ask that all relevant stakeholders work together to find a flexible solution to this daunting regulatory challenge.

Thank you your time and attention and we look forward to your questions.

DR. BERTRAM: Thank you, Mr. Durgin.

Our next presenter is Dr. Paul Tornetta. As previously introduced, Dr. Tornetta received his bachelor's degree in chemistry and mathematics from Franklin and Marshall College in Lancaster, PA. He earned his medical degree from SUNY Health Science Center at Brooklyn, New York, where he also completed his internship and residency in orthopedic surgery, followed by a fellowship in acetabular/pelvic fractures at the Hospital of the Good Samaritan in Los Angeles. He is currently the Professor and Chairman and Residency Program Director in the Department of Orthopaedic Surgery at Boston University School of Medicine and the Director of Orthopaedic Trauma for Boston Medical Center. The title of his presentation: "Clinician's Perspective – Priorities Related to Orthopedic Trauma Devices."

DR. TORNETTA: I'd like to thank the FDA for sponsoring this workshop and for allowing me to participate in it. My job is to talk to you about the clinician's perspective and priorities related to orthopedic trauma devices. My name is Paul Tornetta, I work at Boston Medical Center.

These are my disclosures.

The incidence of fractures is actually quite high and inpatient fracture management with surgery is about five per thousand. Infection can be as high as 35% and it's a real problem. Some fractures are more at risk than others. Open tibias, particularly if there's soft tissue defects that require flap coverage, infection rates are as high as 40%. Complex periarticular fractures like tibial plateau and pilon fractures in the 20% range.

Are there any new thoughts about infection? Well, a quick search would come up with basically all of these articles and you can see there are an abundance of them. And they focus everywhere from soft tissue to timing to antibiotics, but very little on implants.

This workshop has already highlighted the current state of infection and the knowledge gaps for both acute traumatic injuries and osteomyelitis.

Our decision points, as you've heard, have to do with the host, how healthy is the person, and then a lot about the fixation. Is it a nail or a plate? Is the fixation stable? How's the alignment of the limb? Is the soft tissue okay? Is there a graft or is there a substitute?

And hardware retention success is about 60 to 70%. Now, this is patients who get infection early, not late infection, but early infection in the first few weeks. Smoking does predict failure and it seems like nails are a little worse than plates in lower extremity, a little worse than upper extremity. But keep in mind that success is defined here by union, and about a third of these implants will reinfect over time because the truth is the hardware is part of the problem.

To reduce infection, we have to reduce colonization. Once bacteria get onto the device, we have a problem that's very difficult to solve, as you've heard. So our perspective, clinicians, these are horrible problems. These change lives and even end lives. They change families' lives too. And essentially, as a clinician, I would try anything reasonable to avoid this problem for my patients.

This is an off-label use of antibiotics, this is vanco powder being made into a little bit of a paste, but we don't have really antibiotic-coated implants that can help give it a high antibiotic level locally, so we place it in. This is a plate that's placed into a relatively small incision with pretty good soft tissue, but even so, this can get infected. It would be a disaster for the patient. So here you can see those plates covered with vanco paste, and this will actually help to prevent infection. The recently reported metric study of vanco has shown a significant drop in gram-positive infections when vanco is locally applied around the wound.

Open fracture is another very difficult problem. Here, you see a devitalized piece of tibia, but when that piece is removed, we've got an exposed nail that needs to be covered. Again, if we allow this to get colonized, this patient could have a very serious problem.

So here's case number one, and I'd highlight the fact that oftentimes in these conferences you see something referred to as case number one. I don't want you to think that way because this is one person. It's actually a person I know fairly well after taking care of them. It's someone I care about and someone I like very much who deserved to have a better outcome than what they had.

He's a 26-year old father. He's a manual laborer. He came to me with bilateral open tibias both infected at about 2 months out. These are deep infections. The other side was a little bit easier to manage, but on this side, you can see on the left, we put in very small beads to get a high antibiotic level and a high kill and then later, more debridement and a large spacer underneath the flap.

Here he is healed. Well, we had to do a graft. We dynamized that nail because that helped him to heal and at 16 months, we have these beautiful looking X-rays. And we can pat ourselves on the back and say, "Wow, we did a great thing for this patient," and we did. But the patient doesn't quite see the same perspective because these things take a toll. This same person is now out of work, divorced, and lost their home. Not an outcome anybody would want.

Here's another person, another person I care very much for, one of my patients, really nice guy, 54-year-old attorney with three children. He's a very, very active skier. In fact, basically, if you said, "What do you live for?" it would be to ski, and also a hiker. He came to me with this closed fracture that was pouring out pus from the medial side. You can see a large plate there. The wound was completely devascularized distally and a lot of dead bone.

This is after we did multiple debridements, cutbacks, and put a flap bond on top of a spacer, so a few debridements, flap, antibiotics. Here you can see after the spacer's removed with a delayed graft underneath the flap, and we did get him to heal. At 9 months, he looks like this. He was able to walk, he could full weight-bear on it. A CAT scan determined that he was actually fully healed, he had good bridging callus.

But even with that, he took a hit. He's 54. He's been 9 months without using the limb completely normally. He had difficulty walking distances. He lost clients from not being in court, not being able to manage his practice well, and he's not able to do many of his hobbies. Most important to him, he can't ski yet and that's a very depressing thing for this particular individual.

So I would have you ask yourself a question: What's it worth to avoid this? What would you give to have someone you love not be in this position? Almost anything. Remember, the costs here are patient suffering, family suffering, and there's real dollar cost, too. The estimates are between 50,000 and to over $200,000 in overall cost to get someone like this who's infected back on their feet. They lose work and there's disability for life in some cases. And although people have tried, I don't really believe we can put a fair estimate on this loss to society.

So to improve, we have to get new technology. We need to improve everything that we do from soft tissues to implants. So how do we prove technology? Well, we need research. You can see a nice forest plot on the right and it would be great if we had that many studies looking at a particular problem, but that just can't happen for this area of research. We have to use animal data and sparse human data. What should be our burden of proof?

Infection is dichotomous. Studies are fragile. We need huge numbers and in some cases, if the rate is not that high, almost impossible numbers to get in a reasonable way to

prove something out. And you'll hear more about that from my industry partner.

But even then, a few infections can change the statistics. This is the best trial. This was the one that got rhBMP2 approved for use in open tibias and the relative risk reduction was 59% and overall there were about 41 events, you can see the chart here, with a p-value of 0.02.

Well, think about how these things are dichotomous and if these 12 were 15 and 29 were 26, so if we flipped three events in each of the arms, we'd actually drop the relative risk reduction from 60% to 40% and lose our clinical significance. Well, at least our statistical significance. Now, should we be reliant on a p-value of 0.05? No. Should we be reliant on a relative risk reduction of 50%? No. That study was followed up by a very similar study that actually came to a different conclusion. Almost the same number of events in a very similar number of patients, but more evenly distributed, which said well, maybe this is not a real thing. Now, we don't have postmarket surveillance on this device, so we have no idea what the reality of the situation is.

Now, 50% relative risk reduction is sort of the standard in medicine. Is that something that we should apply here? I would say no. I would very clearly change my practice for one less infection a year in my patients because every infection is horrible to that person, to that person's family, and to the person having to take care of them.

So a good clinician, like you see here, what's she thinking? She's thinking, "Is there a chance that this new technology will work, and is it safe?" Does she care about a 50% relative risk reduction or 25% relative risk reduction? No. She just cares that it's safe and it has a chance to avoid infection in her patient.

Think about combination products, antibiotics with a nail or a plate, proteins that are included into some device. Maybe they induce healing or avoid infection. And smart implants, what are we going to do about these things? We think about biologics in

coatings. Safety and efficacy are both necessary but they're independent events in large case, right? So we don't have to know that something is completely effective with a high relative risk reduction. We need to know it's safe to get it to market. I can envision using animal data for both safety and efficacy, doing a small very controlled human trial for safety, and then maybe using real-world data to determine whether a label is indicated or not. And if it decreases infection risk by some small percentage, clinicians may opt to use it if it's cost-effective.

What about electronics, smart implants, additive manufacturing? These are all coming down the lines and they'll have to be dealt with by regulatory bodies. I recognize this is not an easy thing to do, but imagine if we could put a pH sensor in a nail and pick up early infection by the change in pH, potentially improving the care of these patients by jumping on the infection much earlier than we would ever know otherwise. Other ways of manufacturing, changes at the local environment, I could see these being validated with animal studies for safety and efficacy if they provide very little mechanical changes to the implant.

So the clinician perspective. We are very clearly patient advocates. We want to avoid infections, we don't want to treat infections. We're willing to try things that are safe, even if they are not exactly proven out to be completely effective with a high relative risk reduction. It is not a warranted way to look at these problems. Every infection is bad and any chance we have to drop that percentage is worth taking. We want to do better. We need new pathways for new technologies to avoid this kind of bone resection for an infection that maybe we could have avoided.

Infection is a terrible problem. People truly suffer. Their lives are irreparably affected. We have to evolve our thinking, understanding that safety is the main priority, but animal data, small human trials, and postmarket evaluation may be methods that we

can use going forward to get things to market to help patients to avoid infections while still keeping them safe.

Thanks very much for having me. I really appreciate the FDA putting on this workshop trying to work on this very challenging problem.

DR. BERTRAM: Dr. Tornetta, thank you very much for your insights.

Our next presenter is Joseph Ferrante. Mr. Ferrante is Vice President of Research and Development, Trauma/Extremities and Limb Restoration and holds a bachelor of science in mechanical engineering from Christian Brothers University. He is currently on the advisory board for Christian Brothers University engineering programs. He has 32 years of experience in orthopedics design and product development. He has led the trauma/extremities and limb restoration development team at Smith & Nephew for the past 22 years and holds 35 U.S. and international patents for various hip, knee and trauma products. The title of Mr. Ferrante's presentation: "Trauma Devices-Industry Perspective: Orthopedic Device and Regulatory Challenges in the United States."

MR. FERRANTE: Hello. My name is Joe Ferrante and I am the Vice President of Trauma/Extremities and Limb Restoration Product Development at Smith & Nephew. Welcome to my presentation "Trauma Devices-Industry Perspective: Orthopedic Device and Regulatory Challenges in the United States."

I have no financial relationships to disclose and I am a paid employee of Smith & Nephew.

Today, I will take you through how the industry makes program decisions and give you an overview of how we approach bringing on a new program. I will review what goes into the process before a final decision is made to onboard and commercialize a program. It is beneficial for you to understand this process and understand the impact regulatory and clinical processes have on it. This is especially important to small niche programs for anti-

infective and antimicrobial products. I will then review a comparison of the U.S. and CE regulatory process and talk about the challenges for making a decision to go regional or global on a product. I will review the cost and show how the process affects industry decisions and close with some areas that this working group can focus on to improve the process, helping make the decisions more straightforward for industry.

In the next three slides I will take you through the decision process for program selection and show you what is done before a program is ever accepted as a commercial program.

The first step in any program is to identify the problem to be solved. Selection of a product may be dependent on if the product will prevent colonization, kill an infection, how long it elutes or stays on the device, and how long it will be active on the device. A company then looks at the market size opportunity, determines if this is a niche product or larger market product, and determines the potential impact that this type of device will have on the market. We access all of the available technology options and anticipate the risk of other technologies overtaking the chosen technology. We access the length of effectiveness of a device and regulatory path. Finally, and most importantly, we access any risk associated with patients. All of these things are associated with return on investment to a business. Remember, industry wants to solve these problems and improve people's lives, but it is important to understand that industry is a business and businesses make decisions on if a product is feasible. As we look to improve this process, keep in mind the regulatory impact, timing, and decisions of how we approach development of these types of products.

The following is a look at the various options and likely regulatory paths for development. The three selections in pink on the left will probably qualify as Class II products and involve delivery instruments, surface modifications, and other methods that

do not involve combination products. They may or may not be as effective as the right side: antimicrobial, antibiotic, and antiseptic. These options are a more difficult path. They may be on the market in other countries, in process through venture capital companies, or being developed by major medical companies. The reason I show this is the opportunities on the right have the largest potential benefit and the longest path to market, potentially preventing them from being a product. Large companies sometimes take a buy versus make development decision for these products because of the risk and timing. If small companies run out of program money, the products may never exist.

Before we move on to the struggles industry has with the regulatory process, let me show you the amount of pre-work that is sunk into a program before it is ever accepted as a commercial program. There is a vast amount of time and effort spent on pre-work for programs including in vitro testing, both mechanical and biologic, and in vivo testing in large and small animal studies. This work is performed to both prove technologies and to help reduce the time to market showing safety and potential product efficacy. In some cases, it is the only way of showing certain types of data, for example, colonization reduction data vs. infection reduction data.

So let me review the struggles industry has with program selection and then we will show the regulatory process effects. The time to market is the biggest killer of programs. Companies sometimes do not have the stomach for extremely long-term programs unless they are very large companies.

This minimizes the number of programs submitted. Market size and opportunity are factors. Claims have the biggest impact on opportunity. Whether a product is only 20% effective, if it lasts 1 day or 20, does it reduce infection or prevent colonization, all affect the potential success of a product and are critical in the regulatory process. These claims can have significant impact on the timing of a program. It is clear that companies want the

quickest path to market with a safe product. Safety is not up for discussion. Safety has to be addressed.

One critical factor that stops companies from moving forwards is the acceptance of the family. Does one nail apply to all nails? Does one plate apply to all plates in a family? The potential of PMA supplements has to be considered and can have a great financial impact.

The primary indications in trauma is fracture healing. The need for the device after healing is significantly less and different from the recon-type device that is functional for life. Once healed, a trauma device is ineffective and can be removed. This needs to be considered in the regulatory process and can greatly affect the study timing.

Finally, safety versus efficacy needs to be evaluated. The ability to show infection reduction is sometimes lengthy and not the intended purpose of the design.

If you look at the EU versus U.S. regulatory process, EU approval is based on demonstration of a product meeting the general safety and performance requirements established in the MDR. This includes comparison to equivalent devices or inclusion of device-specific clinical data. The U.S. process requires demonstration of substantial equivalence [Class II, 510(k)] or safety and efficacy (Class III and PMA). It is not inclusive of the family of products. Postmarket data is also collected but not used as part of the regulatory approval process.

Let's take a look at an example in the U.S. and clinical process. If you look at the timeline to market in the U.S. process for a selected trauma device, the longest time is the submission date to finish of an efficacy study. The time is approximately 6 years and costs upwards of $8 million. This does not include development cost, timing or testing or preliminary animal studies. It can also vary from 400 to 2,000 patients depending on percentage of effectiveness achieved. Many programs are not cost effective at this point

and are not pursued.

The EU or CE process is significantly less with respect to timing and cost. It focuses on a safety study versus an efficacy model. The time is approximately 3 years to market sell of the product. The cost and timing are significantly less at $2.5 million. The only addition is the use of registry data and PMS data after the product is on the market.

So I've reviewed the process and the different requirements for the U.S. and CE regulatory processes. I hope this has given you some insight to what we look at in selecting and developing a product. Let me suggest a few areas we should be working as a team to help improve and make this area of focus more attractive to industry.

Number 1, distinguish the differences for regulatory path of antimicrobial versus antibiotic combination products. Not every product is looking to kill an infection. Trauma wants to keep it off the implant until healing, allowing the surgeon to use the arsenal of antibiotics on the market. Once healed, the trauma device can be removed if needed.

Number 2, look at combining studies for CE and U.S. regulatory processes. It is critical that we look at one-study versus two and align FDA and CE processes. This can cause companies to stop U.S. market focus and push towards regional OUS products.

Three, look at functioning and timing of the product treatment. How long is it active and how long is it needed?

And four, assess families and other areas that the product can be used and determine if one study can be done to cover all products. These key areas of focus are critical to the selection of whether industry brings on a development project. I believe that this working group focusing in these areas will help to make these type products more attractive to our industry. Thank you.

DR. BERTRAM: Thank you, Mr. Ferrante.

Our second to last presentation comes from Dr. Michael Daley. He graduated with

degrees in experimental pathology and medical sciences, specializing in tumor biology and immunology at Washington University School of Medicine (Pathology) and University of New Mexico School of Medicine (Pathology). He completed a 4-year post-doctoral fellowship in biochemical and molecular immunology, followed by 2 years on the faculty in the Department of Biology at M.I.T. In 2013, he formed OrthogenRx, Inc., focused on the development and commercialization of intra-articular hyaluronic acid products for the treatment of osteoarthritis knee pain. Prior to founding OrthogenRx, from 2000 to 2006, Dr. Daley had received over 36 injections of IAHA with good results, and in 2010 he underwent bilateral staged (1 week apart) knee arthroplasty. Over the course of 15 years because of PJI, he has experienced seven surgeries with one to two additional scheduled, medicated with ciprofloxacin for 22 months, twice experienced peripheral neuropathy (AE of Cipro), 4 DVTs, and considerable limitation of mobility and average daily activities. His presentation: "Patient Perspective on Orthopedic Medical Devices and Potential Solutions".

DR. DALEY: My name is Michael Daley. I have a Ph.D. in medical sciences as well as post-doctoral training and formerly a member of the faculty at M.I.T. Today I join this prestigious panel, not as a scientist, a subject matter expert, or even an entrepreneur, but as a patient that has had to endure the consequences of periprosthetic joint infection for over the past 12 years.

My journey, like many others, started with multiple sports injuries leading to four arthroscopic debridements and one surgical attempt at a meniscal repair. I have been on the fast track to develop severe OA, dating back to 1990. My left knee was the first to develop clinical OA and I was able to manage the pain with nonsurgical interventions, oral analgesics, moderate exercise and occasionally, even injections. My goal was to reach over the age of 60, 65 before I was even to consider a knee replacement, hoping to avoid a revision in my mid- to late-seventies.

By 2009, X-rays demonstrated that my right knee had also developed significant joint space narrowing and pain and my left knee was bone on bone. My personality is an "all in" approach, so after extensive research and networking, I identified where I might want to have surgery performed and by whom. I opted to have a staged bilateral knee replacement, spaced a week apart, at a major institution in the greater Philadelphia area.

In preparation, I seriously took my charge and lost 75 pounds and did 3 weeks of preoperative physical therapy to optimize outcomes. For 3 weeks post-knee replacement, I was in such pain at night that I was sleep deprived and hallucinating, which significantly interfered with my recovery. Despite informing my surgeon of any inappropriate pain management, he was dismissive and it was almost 2 months before I was able to sleep through the night.

Patients are individuals and have different perception and tolerance to pain which must be appreciated. And while the heightened awareness to opioid addiction is warranted, this should not preempt an efficacious, short-term acute treatment for pain management, if appropriate, so as to avoid associated morbidity. This patient's experience says a judicious utilization and close monitoring or clinical follow-up is a much better alternative to optimize patient outcomes. In my case, ASA made my recovery delayed 3 to 4 weeks.

I experienced my first deep vein thrombosis at 90 days post-op, which is often invisible to the orthopedic surgeon but not to the patient. Following my bilateral knee replacement, my flexion was a hundred degrees on my left and a hundred and five degrees on my right knee. However, 40 months post-op, I started to experience severe pain, swelling, and reduced flexion of my left knee, with only 85 degrees flexion. After several consultations, one of which my X-ray was held up and I was told, "Look at that knee, perfect alignment, I've done nothing wrong," the X-ray was doing fine but the patient had severe

pain. CBC and sedimentation rates were normal, although my CRP was elevated two- to threefold.

Based upon the loosening observed on X-ray of the tibial compartment, the recommendation was to do a revision with a longer tibial stem. A partial revision was performed and I received a call 2 days after discharge from the resident stating that one of eight cultures was positive, but that the infectious disease consult had concluded that it was most likely a sampling error. They prescribed a cephalosporin, but I then insisted on a direct infectious disease consult. And with that consult, the speciation was completed the following week. The final culture reported identified *Pseudomonas aeruginosa*.

I was then placed on 60-days course of Cipro, not understanding why *Pseudomonas* could ever be possibly a sampling error. At my 60-day follow-up with my orthopedist, I argued that since I was tolerating Cipro, another 60-day course may be warranted. While on Cipro, my CRP returned to normal and with physical therapy, my flexion again improved to almost a hundred degrees flexion. Within 3 weeks of stopping Cipro, I again developed pain, swelling, and continued loss of function, 80 degrees flexion, and an elevated CRP.

I was aware of Dr. Parvizi's work and others, and actually had previously provided copies of these reprints to my surgeon suggesting that this might indeed be PJI. These were summarily dismissed and he instructed me to continue physical therapy and return 90 days later. I then sought a second and third opinion, both of which agreed that it was likely that my joint was infected. And naturally, Dr. Parvizi was a little bit more emphatic and said he was 99.99% sure I had an infected knee.

I was then quickly scheduled by Dr. Parvizi for a two-stage revision, which was well tolerated given the history and my age. A massive *Pseudomonas* infection was discovered in the joint and medial to the joint, as well as communications of 8 to 10% of these along the tibia and 6 to 8 cm along the femur. Ironically, I received a text reminding me of my

90-day follow-up from my original surgeon's office while I was in post-op following the permanent revision.

Despite a manipulation under anesthesia and continued physical therapy, with all the scarring, I only achieved a final 70 to 75 degrees flexion post-surgery. This has significantly impacted my daily activities, with simple activities such as climbing stairs, rising out of a chair, and entry into cars, not to mention the father-daughter dance at my oldest daughter's wedding. During all these treatments, I have also experienced a total of four DVTs and peripheral neuropathy related to the Cipro.

Almost 5 years later and just 6 months ago in May of 2020, I experienced a fibrous mass in the soft tissue approximately 7 to 8 mm distal to the patella in the thigh and 4 cm medial to the prior incision scar. It was an abscess that started draining an average of 2 to 4 mL of sanguineous pus every other day. It stopped when I was placed on Cipro again, but recurred after 3 weeks of ceasing antibiotic. I had surgery July the 7th for a possible second stage arthroplasty and/or debridement. However, no active infection was observed, but a fibrotic area was identified, indicating a prior active abscess. The area was extensively debrided and no arthroplasty performed. A synovial fluid sample was drawn which was negative. No antibiotics were prescribed at the time, but the abscess appeared 5 weeks later, which was confirmed under ultrasound diagnostics.

Under ultrasound guidance an abscess was tapped and 4 mL drained, growing *Pseudomonas* with only intermediate susceptibility to Cipro. Ultrasound also indicated the abscess might be communicating with the joint. So therefore, another surgery was scheduled on October the 20th to include an arthrotomy and again, to rule out a joint infection and possible revision. No infection was noted on the synovial fluid sample or on cell count or frozen section biopsies of the synovium. No revision was therefore performed. A follow-up to remove sutures and schedule a possible MRI to map out any soft tissue signs

of infection with a possible antibiotic follow-up is scheduled later this month.

In conclusion, I believe PJI is a relatively common occurrence which is grossly underappreciated by the orthopedic community and could potentially be chronic in nature. More sensitive techniques and reports have recently suggested that over 80% of all non-infected early joint failures can be demonstrated to be infected.

Secondly, clinicians should embrace and incorporate patients that strongly advocate for the treatment, incorporating them into the clinical treatment team. It is an opportunity to be transparent, inclusive, and optimize outcomes.

Finally, patients must advocate for their own care, be informed, and respectfully challenge their healthcare professionals, not ignoring their extensive training and experience, but to make sure they are receiving the right and timely treatment for them. Thank You.

DR. BERTRAM: Dr. Daley, thank you for presenting your experiences.

Our final presenter is Mr. Michael Egge, who is the father of Olivia Egge, an osteosarcoma survivor who has suffered from a prosthetic infection. Mr. Egge is a partner at Latham & Watkins in Washington D.C. He is also a founder of the Osteosarcoma Collaborative and an avid advocate for pediatric cancer research because of his daughter's experience. He will present the "Patient Perspective on Orthopedic Infection."

MR. EGGE: Hello, my name is Michael Egge and I'm here merely as the father of Olivia Egge, an osteosarcoma survivor who has had now two full revisions of her knee, half her tibia, and some of her femur in her right leg. As you can see from this slide Olivia is a force of humanity, but I won't even attempt to describe here, as time is short. Suffice it to say that despite her handicap walking today, she is doing well as a second-year pre-med student at the University of Virginia. My comments will focus on sharing Olivia's journey with orthopedic infection and the critical need for solutions from a patient perspective.

Olivia's journey started on February 3, 2017, the day she was diagnosed with osteosarcoma in her tibia just below her right knee. She had her first limb-sparing surgery on April 27 of that year and received a metal endoprosthesis, aptly called a mega-prosthesis given its size. From a surgical perspective, everything went great until almost 2 years later, when in February 2019, Olivia started feeling pain and swelling in her right knee, indicating an infection of her metal. On March 5th of 2019, Olivia had a complete debridement surgery to clean her prosthesis and surrounding tissue of bacterial infection, and then went on an intravenous dose of antibiotics for 6 weeks.

We then entered a long period of uncertainty as there were conflicting signs suggesting the presence of continued infection but also the possibility of resolution. We saw the very best doctors to try to plan whether we needed another painful and invasive revision or to wait it out in the hopes that the infection was resolving. All the tests we tried, including testing for fragments of bacteria DNA, were inconclusive. Olivia started her freshman year at Virginia walking straight-legged in a brace and continuing PT. Not long after that, the drainage in her leg returned and it became apparent that her prosthesis remained infected after about 10 months.

Throughout this time, we searched high and low for solutions. What we learned was incredibly frustrating. First, we learned there are no known cures for prosthetic infections. You either catch it early before a biofilm develops or you replace the metal. Second, modern medicine today does not offer an antibiotic that resolves these infections and obviates the need for more surgery. Third, we learned there are a few antimicrobial-coated products being developed, but none are FDA approved.

We knew that the next revision may be Olivia's last chance at saving her leg. So we located a silver nanoparticle-coated prosthetic available in Germany from Implantcast and secured permission to import it for Olivia. It is not considered a lock at avoiding infection

altogether. There are devices in development that offer better antimicrobial characteristics that many of you here surely know more about than I do, but they are not yet approved.

For patients like Olivia, we understood that her chances for recurrence after another revision procedure was extremely high. Getting every seed of bacteria out of that much of her leg and controlling the infection was going to be very difficult. We were desperate for a solution and believe the silver-impregnated implant materially improves her chances against recurrence.

By February of 2020, we moved up her revision procedure to March 5th and started a series of four surgeries to replace her metal and resolve the tissue impairments caused by infection. Each of these surgeries over the course of three months ran 5 to 7 hours in length. COVID didn't help. It was traumatic, as evidenced by this picture on the right. We knew replacing her metal was a complicated exercise and she lost some bone as a result, making risk around further surgery, God forbid, higher. But the tissue repair and the impact on what is left of her leg has left its mark, as well.

We are hopeful that the science and regulatory issues to getting new solutions to market are overcome as quickly as possible so that a true solution is available for Olivia and others as they confront these infection control issues. In Olivia's case, we don't know if we can successfully do another revision and if there are no better implant alternatives, amputation will be her only option.

Finally, I want to emphasize that Olivia's situation is unlike others in one important respect. There is no other way to say this, she is privileged. We have the means and resources to find the silver-impregnated prosthesis in Germany and to get it imported. Most kids do not, which underscores the need to create options beyond amputation.

I close on a happy note with a picture from the production set of the movie Clouds that was released recently on Disney+. Olivia's Make-A-Wish wish was to be a part of this

movie, which no doubt will create awareness about osteosarcoma and its impact on teens. I hope you get a chance to see it as it is beautifully done and a great story. Olivia is here with two of the stars she shot a scene with. Thank you for all this group is doing to help kids with osteosarcoma, as well as the many other people affected by prosthetic infections.

DR. BERTRAM: Thank you so much, Mr. Egge.

Now it's time to turn to all of our presenters from Session 4 for our last presenter discussion. The moderators for this will be myself and Dr. Ken Urish, who is an associate professor at the University of Pittsburgh Department of Orthopaedic Surgery. He is an associate medical director at the Magee Bone and Joint Center and the director of the Arthritis and Arthroplasty Design Group. He is involved with a number of prospective clinical studies aimed at improving the treatment of surgical infection, including a series of FDA studies investigating new antibiotic and delivery devices.

Dr. Urish, I'm ready if you are.

(Off microphone response.)

DR. BERTRAM: I think you're on mute.

DR. URISH: You're next.

DR. BERTRAM: So I will actually -- good to have you. Again, wonderful presentation and -- Mr. Egge. And what a diverse way to end a great workshop. Again, diversity and issues and discussions and sort of what side of the table you're on has been peppered throughout, but I think this last panel really is sort of an exclamation point to that.

And with that, as I -- again appreciating no matter what side of the table, if you're a regulator, a physician, a researcher or whatever you're doing, ultimately the common thread between all of us is the patient and really an outcome, a positive outcome for the patient.

And with that, before -- we have quite a few questions from the audience. Before

kicking over to those, though, I just want to give an opportunity to Mr. Egge and Dr. Daley. The patient perspective. Again, whether as a father, as a patient yourself, you're the common thread in all of this, or one of the many common threads, and I just wanted -- after hearing everything you've heard today from the various sessions, any thoughts, comments, insights, future directions, I appreciate anything you may have for all of us.

Dr. Daley, I believe you are on mute.

DR. DALEY: I'll chime in very quickly. Ironically, while I was going through the beginnings of my journey, I was starting my company and submitting my regulatory filing to CDRH and actually, Larry Coyne knows me all too well. Never on this side of the table with him.

But in any case, I'm very familiar with the process and CDRH, I think, does a great job of collaborating and interacting and having some creative input on how to get these products approved. The 510(k) process has been under review, they now have a de novo process, these are all things that we've got to take -- we can potentially take collectively away and move forward.

But what I'm a little disappointed about this panel is there's no representation from CDER or CBER. So CDRH has limited capabilities of what they can do if it's all mechanical in a device, you can talk to them, but they need to collaborate with the other centers. Anything that you're including, an antibiotic or whatever it is, really needs that input. And so I would ask that we start having that dialogue with other centers of FDA.

And in addition is the insurers. All of this, companies, at the end of the day, have to find out that at least they can sell their product, they don't have to make great profits. But the insurers aren't represented, which would include CMS. So I think that a future panel may include them as another very important stakeholder.

DR. BERTRAM: Dr. Daley, I always speak on behalf of CDRH. I greatly appreciate the

insights and future directions and who to include. As I noted in the beginning, we have limited time here and I fully agree with you, the collaborations that need to exist between the centers and this is, again, I think a great springboard for those future workshops and those sort of joint presences and considerations, so thank you.

Mr. Egge.

(Off microphone response.)

DR. URISH: Mr. Egge, you're also on mute.

MR. EGGE: How about now, can you hear me?

DR. BERTRAM: You're very faint.

MR. EGGE: Okay. No good. How about this?

DR. BERTRAM: That's a little bit better. If you can go louder, great, but I think we can hear you with that.

MR. EGGE: Great. I'll be loud --

(Audio feedback.)

MR. EGGE: I just wanted to say thank you. I believe this kind of collaboration is absolutely -- I'll tell you, as a parent, going through the cancer, I thought the cancer was bad, I thought that was hard and I never expected that bacterial infection would be this difficult. And so anything that you do to address the adoption and approval of the medical centers that might have a solution around microbial infection is greatly appreciated, particularly by me and I'm sure the entire patient community.

DR. BERTRAM: Thank you.

Dr. Urish, unless you had something specifically, I was thinking we would go to the questions from the audience.

DR. URISH: Yeah, one quick thing, this was -- sort of some of this is for the clinicians that are on the panel and this kind of came up in Dr. Tornetta's talk, and it was kind of a

circling theme throughout. You know, you brought up the use of off-label use with the addition of antibiotics in the cement and maybe for everybody else out there, how often -- for the clinicians out there, but surgeons -- are you using off-label devices like antibiotics in the cement? And then how are you balancing out the antibiotic stewardship versus the potential benefit since it's not studied as much if it's efficacious or not? This is for all the surgeons out there.

DR. TORNETTA: It's Paul, I can start. So I've been using vancomycin just with normal saline to make a putty for maybe 10 years now. It's very locally applied. There's some data that came early from thoracic surgery that showed it to be relatively safe in sterna ribs and I basically applied it from there. And that's been shown in multiple areas, not necessarily the putty/paste but the injectable or putting it in in spine and other areas.

You know, that all led to the study that Mike Bosse presented on vanco, which is really good, and the way I view most of this is these are very localized environments. So you know, if you put something on top of a plate around the ankle, it's just not going to become a very systemic problem and it's not a large dose, but it's highly effective, I think, at those local environments. So we are, right now, having to do that on our own and the point you make, Dr. Urish, is excellent, is that we're using things off label without the safety component except for our best judgment, right, and then that's what off-label use always is, it's the surgeon's best judgment. So I've done that, I think, with relatively decent evidence. There's animal studies around injection of gentamicin and vancomycin that seemed to be safe, but that was the safety data upon which we acted, right, as groups of surgeons.

So I think going forward, that highlights at least my thought and I think what I heard from multiple other people, including the patients on the panel, is that the safety and the efficacy likely need to be separated in some way because that would give guidance to surgeons around making sure we're safe while leaving open the opportunity to take a

chance on something that might do better. And I think that principle, you know, is something I talked about, but I heard it from six other people today and I think that it's excellent that you're highlighting it, thank you.

DR. IORIO: This is Rich Iorio, I can't agree more. And this leads into another topic which is very much more difficult. We've shown that using vancomycin powder locally delivered to the wound along with povidone-iodine soaps in high-risk patients decreases that infection rate 20%. Yet we're told by the CDC that we don't want to be giving much more antibiotics to these people and that our stewardship needs to be more attuned to maybe one dose of antibiotics per perioperative episode and then that we shouldn't extend antibiotics later. Yet, now our data is showing us in the high-risk patients that are revisions, that extending antibiotics orally for 3 to 4 weeks after the procedure in revisions of the high-risk patients actually decreases our infection rate another 20%.

So this gets to Paul's point, you know, when does the safety impact the results that we're trying to obtain when we know that these things work, right? So we're running into reluctance from our infectious disease colleagues, yet we have very solid evidence, albeit with small numbers and not statistically significant, but certainly financially relevant and as we saw from the attestations of these patients, clearly personally relevant. So we need to fund these studies at a higher level, we're trying to do that now, but we need thousands of patients to obtain statistical significance and yet I think you've got some pretty high-level clinicians here who will tell you that this stuff works. And I agree that locally delivered antibiotics probably are not going to cause a systemic super bug that's going to kill somebody when we've got very localized biology going on for osteomyelitis or total joint replacement.

Then as a third part of this where you can deliver vancomycin intramedullarily into a bone, both as a prophylactic and as a therapeutic for local infections, that then does not get

systemic at all and may be a good way to go, and I think we need to expound on that more. Henry Clarke has shown this down in Mayo Arizona for joint replacement. I'm sure it's probably a good methodology for osteomyelitis. Trauma, as well. So something to think about.

DR. BERTRAM: Sort of a segue on this discussion and I heard quite extensively, and I'll admit this was quite an educational experience for myself, the considerations and sort of the evolution of understanding of the role of biofilm and sort of the complexities there. Are there thoughts, is that better understood, there's a better appreciation for the need for local administration or is it just appreciating it's that much more complex? How does the panel see sort of that interface with what at least I understood to be a significantly evolving and a better understanding of a pathology associated with this issue?

DR. PARVIZI: Dr. Bertram, can I make a comment?

DR. BERTRAM: Sure.

DR. PARVIZI: So having served on the CDC guideline committee for 4 years and poring through a lot of the literature related to antibiotics, I totally understand why CDC is so sensitive to liberal use of antibiotics in medicine. And there is plenty of evidence to show that antibiotics alone are definitely not the holy grail. To address the biofilm, antibiotics are probably very ineffective as we've seen in the past, so we need antiseptic solutions, biofilm disruption technologies that are other than antibiotics, moving into the future.

And as many of the brilliant speakers have already highlighted today, three things that stand in the way of that particular advancement. One is finding the right science, and I think our scientists and surgeons and clinicians are working on that and borrowing experiences from other anti-biofilm technologies such as glass manufacturing and the petrochemical industry.

The second is funding, and industry interest in pursuing such a technology, which is interlinked to the third and the most important part and that is finding a smoother and perhaps less cumbersome and prohibitive regulatory path that allows these technologies to get to market without having to do a clinical trial on 11,000 patients.

So I am personally not an advocate for antibiotics. I think David Lowenstein (sic) showed beautiful data that liberal use of antibiotics are going to be an issue for us and they, in fact, are. Antimicrobial resistance will kill more people than cancer and trauma combined by Year 2050 unless we get our arms around this AMR. ESKAPE organisms are killing 15,000 patients or more across the U.S. on a daily basis.

So in the interest of moving in the opposite direction of just advocating liberal use of antibiotics, we need to think about other technologies that will have a better promise for our patients, like we've seen from Dr. Daley and Mr. Egge's presentations today, and I want to thank both of them for giving us incredible insights as to challenges that we face as orthopedic surgeons today.

DR. DALEY: This is Mike, I just wanted to jump in here and I'm kind of thinking about it. I'm a scientist, I'm a Ph.D., I go on data. So I like to say we know that this works. No, you don't, you've got to have the data. And the way in which to approach this is you've got lots of great approaches, some of which are FDA approved, some of which are off label and unlike in the U.S., we have to have some central repository to gather that data in a registry type of fashion and we have to all have to agree to a protocol for PJI. What are you going to do? No matter what you're doing in intervention, multiple antibiotics, the debridement, two-stage, what are you putting in the temporary joint with, whatever it is. And we have to have a centralized way with an agreed-to protocol so that everybody can sign up for it and the FDA might be able to do a preliminary approval and then have revisited it in a year.

That is common in Europe, and the reason they can do it in Europe is they have

single payers, so they can gather all that information because it's provided to the government, who's paying for this intervention. But we've got to find a way in which to gather the data to make these great decisions on how to move forward. But when everybody's scattered doing their own protocol and developing their own algorithm, it doesn't help the greater community until we can centralize that data. So I would push back that either with the government and FDA or some consortium, come to consensus on how to move forward with infections in orthopedics.

DR. URISH: So following up with all this, some of the themes that have kind of come up to these questions have been getting things to market and with antibiotics, one of the questions from the audience was -- this is maybe for both the surgeons and for the FDA. How do you see the use of these prophylactic uses of irrigation solution in the role with infection control or fighting infections?

So I'll kind of throw this -- you know, it's always hard to get the FDA on the panel, so this might be for Dr. Coyne and for Dr. Bertram. You know, when you have these types of products that are a little bit device and a little bit on the drug side and it's in a combination device, how do you see this kind of coming through?

DR. BERTRAM: Dr. Coyne, I'm happy to start first, but I've been talking a little bit, so if you want to go, just whatever you prefer. So I --

DR. COYNE: Go ahead.

DR. BERTRAM: Okay, so I think I'll put my cap on and one my roles that I have at the Agency is as the jurisdictional officer and I have to figure out -- the first question the Agency is going to ask is what center does this belong to? And then the question is okay, what centers need to be involved once we've figured out who is "the lead." And I think you bring up a great question and a great point in something that some of you may have experienced personally with engaging with the Agency and trying to elucidate how your product works.

And again, I think that's just sort of the regulatory rubric that the Agency has and how we categorize the products.

So to the extent that, obviously, we always want innovation, we want to promote innovation and whether you agree with that or not, believe it or not, that is our intent. But I would say uncertainty in how the product is working, the relative contributions, not only play a significant role obviously in the Center, but then obviously I would think for sort of the industry, the pay, the potential profits that are able to sustain and promote and advance future iterations and continue that development because of wanting to know the pathway, wanting to know what claims are able to be obtained, what kind of -- what can you say about your product. It inherently goes then to the clinical evidence as well as need. But with that, I will pause and allow Dr. Coyne to provide any comment.

DR. COYNE: With respect to the prophylactic use of your irrigation solutions, the considerations that we would be looking for in terms of clinical evidence are basically the comparison of the investigative and the control groups and from the standpoint of elucidating conclusions from any uncertainty. So the prime consideration would be that the similar regimens are found for the investigative and control groups. If you talk about a 510(k) pathway, for example, then you'd be -- typically it would be a comparison to an already legally marketed product. The question that comes on here in terms of from a regulatory standpoint is just making sure that -- to the maximum extent as possible, that the investigative and control groups are comparable in terms of treatment and ovulations and all of the considerations that we're -- that go into a successful clinical trial.

DR. BERTRAM: Okay, thank you, Dr. Coyne.

Maybe a little bit of a tangent, another question from the audience was -- and this sort of piggybacks on Dr. Daley's comment about the other centers and some of the other technologies that are being seen. Dr. Parvizi provided comment to this earlier, as well, with

phage sort of therapies. But specifically for Dr. Iorio, there's a question of have you found that allograft bone and tendons are able to successfully be implanted into an infected field or implanted in high infection risk patients?

DR. IORIO: No. Very rarely.

DR. URISH: Okay, we're getting a little bit of a thing in our chat box here that I think we're running out of time, James.

DR. BERTRAM: In the box, I see that. And okay, I lose track of these things when I'm actually part of the discussion, so thank you very much for keeping me on track.

DR. URISH: I'd like to thank all the presenters and, James, thank you for letting us be around.

DR. BERTRAM: Of course. And just as my own closing remarks, I just wanted to thank all of you one last time. It's been truly a learning experience for myself, as I hope it has been for others. Just a reminder, before turning it over to Captain Peat, all presenters and moderators, please turn on your cameras and don't be shy, beautiful people, beautiful faces. So until next time.

DR. DALEY: James, I just want to intervene that CDRH has really always been leading the charge from the first to adopt the Bayesian solutions, the collaborative nature I found with CDRH. So if anything's going to happen in this field, CDRH is going to be leading the charge and I appreciate what you've been able to accomplish here. This is great and it's a very important issue.

DR. BERTRAM: Thank you.

Captain Peat.

DR. PEAT: Hello again, this is Captain Peat and what I can say is wow, what an amazing day it has been. It is an honor to be able to provide today's closing remarks. I cannot emphasize the importance of today's meeting, and it's long overdue. The

conversation from this workshop resulted in a number of actionable steps and all of these actionable steps will be worked on over the coming months. We will again bring forward discussions in the fall of 2021 that not only addresses concerns raised from today's meeting, but also includes robust discussion on combination products with our colleagues and other centers in attendance. It was our hope today to start at some baseline thinking about the concerns that we have and then bring in our colleagues for additional discussion.

As I'm before you and you enjoying the rest of your day and weekend, I would like to take some liberty extending my thanks to a number of individuals, starting with my special thanks to our master of ceremony, Dr. James Bertram, for facilitating an excellent workshop. Your performance for navigating the various topic areas was stellar.

Also extending my thanks to all of the faculty, as each expert came from various organizations with equally various subject matter as fitting, and provided thought-provoking potential strategies to address associated challenges and foster collaboration centered on orthopedic device-related infection. To our faculty, I challenge you to continue to work with us as all that we have identified in today's workshop will need each of your help to effectively address for all within our orthopedic ecosystem.

I wanted to extend our collective thanks to the following members of the planning team: Dr. Vincent Devlin, Dr. Javad Parvizi, Dr. Paul Tornetta, Dr. Laurence Coyne, and Lieutenant Commander Randoshia Miller. Without you all working alongside me on the development of this workshop during the long evenings and weekends and e-mails after e-mails, this workshop would not have occurred. I owe you a debt of gratitude.

It was a difficult conversation, but a necessary conversation. And anyone who knows me knows that I do not lead by a cloak-and-dagger approach. Visibility and discussion of this topic is most important for our patients.

I also want to thank Dr. Daley, as well as Mr. Egge, Olivia's dad. We hear you and we

are going to continue to move forward positively to effectually change.

I could not leave out CDRH Office of Communication and Education, and my thanks for the external messages on social media and FDA websites and the utilization of FDA TV Studio. My thanks to Peggy Roney, Barbara Richards, who's our director extraordinaire, and the countless others in FDA and FDA TV Studio, the high end of production, for tirelessly editing and making this virtual meeting superior, if not on par to world-class communications forms.

We have made a number of changes as we address as a nation this COVID-19 pandemic and you will stand every step of the way in a system with the implementation of our virtual meeting.

Dr. Maisel was correct in his opening remarks that this workshop would address numerous topics intended to prompt dialogue, discussion, and collaboration. And we will continue with the exchange of information among interested stakeholders, including you, our audience, the over 700 of you who took the time out of your busy schedules for which you are part of the healthcare community, medical device manufacturers, academia, government agencies, and our patients.

I'll close this meeting and for all of next week, if there are any remaining questions or comments, please send to our OHT6-FEEDBACK@fda.hhs.gov e-mail account. In closing, stay safe and have a beautiful remainder of the day with my perfuse thanks for your participation in today's first of many orthopedic device-related infections workshop. Good day and good bye.

(Whereupon, at 1:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

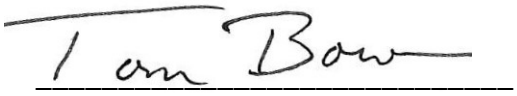
This is to certify that the attached proceedings in the matter of:

PUBLIC WORKSHOP - ORTHOPEDIC DEVICE-RELATED INFECTIONS

November 13, 2020

Via Zoom Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.



TOM BOWMAN

Official Reporter