

Montana State University
■ Center for Biofilm Engineering
Bozeman, Montana

Anti-Biofilm Technologies: Pathways to Product Development

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presentation

proceedings

Abstracts

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Presentation Abstracts

SESSION 1: Medical Device Technologies

What can we learn about medical device associated infection pathogenesis from skin explant models?

Presenter: **K. Scott Phillips**, Senior Biofilms Research Group Leader

Co-authors: Yi Wang, Allan Guan

Affiliation: Division of Biology, Chemistry and Materials Science, Center for Devices and Radiological Health, US FDA, Silver Spring, MD, USA.

In recent years, CDRH has received submissions with a variety of claims related to microbial colonization and biofilm on medical devices. Often the approach to thinking about and testing devices is focused on the novel features of biomaterials that prevent bacterial adhesion, colonization, and/or biofilm formation. However, the interactions that occur in the pathogenesis of infections are complex, involving microbe, device, and host. To better understand and quantitatively assess if and how medical device associated infections can be prevented by novel technologies, we are evaluating ways to include the host as a variable in testing. Our hypothesis is that by better incorporating aspects of the host interaction, we can obtain more realistic estimations of potential in vivo performance. Since we have very limited resources for this research, we began with the simplest possible case—the skin. By replacing plastic with skin as a tissue in antimicrobial performance testing, we found increased challenges in killing and removing biofilm. Due to the topographic nature of the skin as a substrate, we also found that combination physical/chemical strategies were required to remove biofilm more effectively. Based on these results, we are currently investigating differences in antimicrobial performance for devices that penetrate the skin (percutaneous devices). Since these devices are in contact with the skin, in some cases—especially for contact killing or anti-adhesive antimicrobial technology—performance may be more dependent on the properties of the skin itself than the novel features of biomaterials.

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Bad to the bone: Antimicrobial devices in surgical infection and needed standards

Presenter: **Kenneth Urish**, MD, PhD, Director

Affiliation: Arthritis and Arthroplasty Design Lab, Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA.

Medical device infection remains an enormous problem with significant morbidity and mortality. As technology and scientific breakthroughs continue to evolve in an exponential manner, there are many combination products that are being developed to treat and prevent medical device related infections. A combination product is typically defined as a device that incorporates a biologic or pharmaceutical to obtain its desired effect or treatment. Outside of the typical regulatory approval pathway for a device, these devices have a unique set of regulatory hurdles as manufacturer's interact with two separate divisions of the Food & Drug Administration (FDA) on devices (CDRH) and pharmaceuticals (CDER). The FDA is now creating ways to categorize and review these combination products, but there is a need for standards and guidance documents to assure their safety and effectiveness. There are many unmet needs regarding standards for antimicrobial combination devices, including antimicrobial coatings on implants, antibiotic addition to existing products, and antibiotic eluting devices. These topics are important because if device colonization and biofilm form on a device, it typically requires removal with local and systemic treatment to address the infection.

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Antibiotic resistance and biofilm: An overview of research at the FDA Center for Drug Evaluation and Research Division of Applied Regulatory Science

Presenter: **Rodney Rouse**, DVM, Research Veterinary Medical Officer and Associate Division Director

Affiliation: Division of Applied Regulatory Science, Office of Translational Science, Center for Drug Evaluation & Research, Office of Clinical Pharmacology, US Food & Drug Administration, Silver Spring, MD, USA.

This presentation will give an overview of research at the US Food & Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Division of Applied Regulatory Science (DARS). Regulatory science in DARS will be profiled and examples from the very diverse roster of active research projects will be presented. Time will be spent describing projects focused on antibiotic resistance and development of in vitro and in vivo models to assess the ability of future products or treatment regimens to suppress emergent antibiotic resistance. The potential impact of those novel therapeutic approaches on the gut microbiome, another potential reservoir for antibiotic resistance transmission, will also be discussed. Lack of thorough understanding of factors including the contribution of biofilm to resistance development will be highlighted. To actively combat the present antibiotic resistance crisis, a more thorough knowledge of the natural history of antibiotic resistance is necessary. In concluding, observations will be shared on the current reliance on in vitro and crude in vivo modeling for determining and measuring resistance and whether this may be misdirecting present efforts.

Update on methods used to assess biofilm prevention on surface modified urinary catheters

Presenter: **Jennifer Summers**, Masters Student, Chemical & Biological Engineering

Affiliation: Center for Biofilm Engineering, Montana State University, Bozeman, MT, USA.

More than 90 million indwelling urinary catheters are sold annually worldwide and approximately 15% of all adult hospital inpatients will require short-term (<14 days) catheterization. Urinary catheters disrupt patients' normal immune defenses increasing their risk of acquiring a catheter associated urinary tract infection (CAUTI). CAUTIs account for 40% of all hospital acquired infections (HAIs) and are estimated to cost \$2,900 per episode and \$2.9 billion annually. In 2009 the CDC published the "National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination (HAI Action Plan)." The plan identified the top 7 HAIs reported in the U.S., which included CAUTIs, and set incidence rate reduction goals for each. In the 2016 progress report, the CDC reported that CAUTIs were the only HAIs to show no overall decrease of incidence rate between 2009 and 2014. A significant amount of effort has been put into developing novel surface modifications in attempt to eliminate this threat to patient health. However, researchers and regulators are lacking a standardized in vitro test method which accurately predicts the efficacy of the anti-infective strategies. The Burroughs Wellcome Foundation awarded the CBE a five-year grant to develop and validate a quantitative in vitro method that will enable regulators to efficiently evaluate the efficacy of surface modified urinary catheters. Currently, the method consists of a model that evaluates the efficacy of interluminal surface modifications to delay biofilm attachment. This model has been proven to be sensitive to many different treatments and shows promise in being a useful tool for regulators. As continuous improvements are made to this model, future work will also focus on developing a second model to evaluate the migration of bacteria on the extraluminal surface of urinary catheters.

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Animal model for testing anti-microbial and anti-thrombogenic effectiveness of vascular catheter technologies

Presenter: **Nisha Gupta**, Manager, Technology Development, Vascular R&D

Affiliation: Teleflex, Inc., Reading, PA, USA.

Intravascular catheters have advanced in recent years to include various surface modifications such as antimicrobial coatings, hydrophilic coatings, heparin, metals, or other polymer surface modifications. These efforts aimed to minimize complications involving catheter related blood stream infection (CRBSI), occlusion, and thrombosis, which commonly necessitate catheter removal. The purpose of this investigation was to develop animal models for assessing intravascular catheters with antimicrobial and/or antithrombogenic technologies. Sheep were selected as the animal of choice as they offer anatomy comparable to humans as well as gentler dispositions that make them more amenable to frequent handling and judicious post-operative catheter care.

The first sheep model evaluated antithrombogenicity. Catheters were placed through the left jugular vein into the superior vena cava (SVC). After a 30-day indwell period, explanted catheter and vein tissues were analyzed for presence of thrombus accumulation (in terms weight and length) and extent of venous thrombosis (by grading pathological features through histology).

The second model was developed to assess antimicrobial performance, as well as antithrombogenicity in presence of infection, since infection can lead to thrombosis and vice versa due to the bidirectional relationship that exist between the two. *Staphylococcus aureus* was swabbed at the catheter insertion site followed by catheter placement through the left jugular vein into the SVC. After 30 days of placement, in addition to thrombus measurements, explants were also analyzed for amount of bioburden present on the catheter and the surrounding tissue. Both models allowed assessment of antimicrobial and antithrombogenic technologies for intravascular catheters based on quantitative data.

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In-vitro and ex-vivo analysis of vascular catheters for biofilm

Presenter: **Garth James**¹, Associate Research Professor, Chemical & Biological Engineering

Co-Author: Elinor Pulcini¹, Steve Fisher¹, Laura Bickle¹, Marcia Ryder²

Affiliation: ¹Center for Biofilm Engineering, Montana State University, Bozeman, MT, USA. ²Ryder Science, Inc., Brentwood, TN, USA.

Catheter-related blood stream infections (CRBSI) are one of the most serious and costly hospital-acquired infections. Several organizations including the Centers for Disease Control, Association for Professionals in Infection Control and Epidemiology, and Infectious Diseases Society of America have released guidelines for preventing CRBSI. There are two main routes of infection for CRBSI: intraluminal and extraluminal. The intraluminal route results from contamination of the catheter access point (such as a needle-free connector) or introduction of a contaminated fluid into the catheter. The extraluminal route involves contamination along the interface between the skin, subcutaneous tissue, or vein and the outer surface of the catheter. Devising and modifying devices to help prevent CRBSI is an active area of research and development. Device strategies include antimicrobial catheter surfaces for both routes of infection, lock solutions to prevent or mitigate intraluminal infection, and antimicrobial dressings to prevent extraluminal infections. Development of effective technologies requires adequate in-vitro and in-vivo testing, followed by human clinical research. The Medical Biofilms Laboratory at the Center for Biofilm Engineering is involved in both in-vitro and in-vivo testing of devices designed to help prevent CRBSI. In-vitro testing for the prevention or mitigation of intraluminal colonization and biofilm formation can be performed using a wide variety of clinical use scenarios. The number of live bacteria in the catheter lumen can be assessed by removing and suspending the bacteria, followed by traditional viable plate count analysis. Direct microscopic analysis

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of the catheter surface can also be performed using scanning electron microscopy or confocal scanning laser microscopy with fluorescent probes. Evaluation of 24-hour catheter colonization using six species of antibiotic-resistant bacteria indicated repeatable and similar results among species and survival of the bacteria for an additional 32 hours under low nutrient conditions. Although in-vitro testing allows flexible testing parameters under controlled conditions, important host factors cannot be incorporated. These include blood clotting factors such as fibrin, fibronectin, and platelets, as well as immunological factors. These factors can have important influences on biofilm formation, pathogenicity, and antimicrobial effectiveness. Realistic testing of extraluminal colonization is also difficult in-vitro due to the complexity of the catheter interface with the skin, subcutaneous tissue, and veins. In-vivo models allow for device evaluation under conditions that include host factors. Analysis of catheters from in-vivo models for intraluminal colonization can be conducted similarly to in-vitro models. However, for extraluminal colonization, the association of the catheter with the skin, subcutaneous tissue, and veins must be considered. En bloc resection of the catheter and associated tissue and subsequent dissection enables examination of biofilm-catheter-tissue interfaces and host responses. Overall, a combination of in-vitro and in-vivo tests can enable an assessment of new strategies to prevent CRBSI.

SESSION 2: Surface Disinfection Technologies

What's next for biofilm standard methods?

Presenter: **Darla Goeres**, Associate Research Professor, Chemical & Biological Engineering

Affiliation: Center for Biofilm Engineering, Montana State University, Bozeman, MT, USA.

The US FDA defines regulatory science as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products (US FDA, Advancing Regulatory Science). The CBE is committed to expanding the biofilm methods tool box and teaching the biofilm community how to apply these methods to fit their own needs through workshops and on-line videos.

There are different approaches for controlling biofilm in an environment. To date, the biofilm standard methods have focused on efficacy testing traditional biocides to kill the viable cells in a biofilm. Because biofilms are more tolerant to disinfection than are planktonic cells, to achieve the target log reduction in viable cells means the treatment employed will either increase the biocide concentration, extend the contact time, and/or include the use of more aggressive chemicals. In addition to measuring the immediate kill in viable bacteria, another way to gauge biocide efficacy is to determine the time required for the biofilm to recover. In industrial applications, companies have clean-in-place procedures that are based upon the time it takes for a biofilm to recover to the level where the process or product is again impacted. The goal is for the biocide dosing strategy to keep the biofilm at an acceptable level in terms of process performance or product quality. Therefore, a standard method that measures biofilm regrowth after biocide exposure would be a useful contribution to the biofilm methods tool box.

In many applications, removing the biofilm is a practical strategy. Effective removal includes eliminating and/or reducing the viable microorganisms, EPS and all the environmental contaminants that have become entrained in the biofilm matrix. For these applications, for example in cooling towers, piping systems in many industrial applications or in a home, it is not the presence of bacteria that is the issue, none of the examples given are sterile environments, but rather that the biofilm matrix is impeding optimal performance, contributing to corrosion or heat transfer loss, impacting the aesthetic appearance of the surface or providing a haven for pathogenic organisms to survive and/or flourish. In these examples, the goal is to apply a chemistry that removes the biofilm, or simply put, cleans the surface, thereby improving performance, aesthetics, and surface integrity. In addition, if the biofilm is removed, the haven for the pathogenic microbes is eliminated as well. In some processes, removal is followed or paired with a disinfection step. Now, instead of needing to add excess biocide to penetrate the thick biofilm, the concentration of biocide may be reduced to a more reasonable level and the time

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for biofilm regrowth lengthened. A standard method that assesses biofilm removal would also be a useful tool for the biofilm community.

This presentation will provide an overview of potential methods to assess biofilm regrowth and removal.

Translating bench science into policy: How to drive policy toward science and technology

Presenter: **Jennifer Buss**, Vice President Science and Technology Policy

Affiliation: Potomac Institute for Policy Studies, Arlington, VA, USA.

The Potomac Institute for Policy Studies provides nonpartisan, practical, and practicable analysis of science and technology policy to leaders in government, industry and academia. The Potomac Institute is an independent not-for-profit policy research institute. The Institute identifies and aggressively shepherds discussion on key science and technology (S&T) and national security issues facing our society, providing an academic forum for the study of related policy issues. From these discussions and forums, we develop meaningful policy options and ensure their implementation at the intersection of business and government. The Potomac Institute for Policy Studies seeks to (1) anticipate the problems our society will face in the future, and (2) work toward establishing meaningful policy options for addressing these problems before they come to fruition. The Institute is keenly aware that implementation of policy is perhaps the most difficult component in public endeavor. As a result, we do not merely conduct a world class study and provide a report. We roll up our sleeves as a think and “do” tank!

Biofilm claims on EPA-registered products—Opportunities for public health and industrial applications

Presenter: **Elaine Black**, Senior Manager Regulatory Affairs

Affiliation: Ecolab, Saint Paul, MN, USA.

In 2017, the EPA issued a long-awaited guidance document “Methods and Guidance for Testing the Efficacy of Antimicrobials against Biofilm Bacteria on Hard, Non-Porous Surfaces,” providing a framework for companies wishing to make biofilm efficacy claims on product labels. The guidance and accompanying documents focus on biofilms in healthcare and other settings of importance to public health (with the exception of food processing environments). In addition, the documents give clarity on labeling language and the use of the terms “slime” and “biofilm” in industrial settings. This presentation will give an industry perspective of the need for and ultimate use of these new claims in both healthcare/institutional and industrial settings, and will include some relevant case studies. Future considerations for food-processing relevant claims will be briefly addressed.

Navigating the regulatory landscape in bringing hygiene solutions to market

Presenter: **James W. Arbogast**, Vice President, Hygiene Sciences and Public Health Information

Affiliation: GOJO Industries, Inc., Akron, OH, USA.

Hygiene products marketed in the US may be regulated either by the EPA for inanimate surfaces or by the FDA for skin care applications. The skin care solutions are required to comply with cosmetic, OTC drug monograph, or new drug FDA rules, depending on the claims that are being made. Regulated frameworks and constructs significantly determine what industry can and cannot do. They sometimes create conundrums and generally are anti-innovation, making it very hard to change the status quo. This presentation will unpack some of the challenges and complexity of navigating the regulations in successfully launching new hygiene products in the US.

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In this presentation, the product development process will be introduced and framed by the most important success factors. The basic goals of hygiene solutions and evidence around their benefits to public health will also be introduced for context. Specific examples that show issues that may arise by not following the rules (e.g. warning letters) and some of the current challenges will be highlighted. Those examples will include surface sanitizing in restaurants, with the FDA Food Code requiring a rag and bucket process, that arguably creates risks (e.g. biofilms in rags or buckets) and the risk of biofilms in secondary packaging with open refillable soap systems (only regulated out in healthcare). In closing, future possibilities for hygiene to drive biofilm risk reduction that may benefit from new regulatory approaches will be shared.

Standardization and use of uniform terminology in biofilm research—A European perspective

Presenter: **Tom Coenye**, Professor, Microbial Molecular Biology

Affiliation: Laboratory of Pharmaceutical Microbiology, Ghent University, Ghent, Belgium.

Treatment of biofilm-related infections is difficult and while a lot of effort has been devoted to developing standardized models for biofilm susceptibility testing, the added value of using these models in different settings is unclear. Due to the profound differences between *in vitro* and *in vivo* grown biofilms, extrapolation of antimicrobial susceptibility data obtained *in vitro* is difficult, even when standardized methods are used. In addition, the high tolerance observed in biofilms makes it unlikely that antibiotic concentrations that are active against biofilms can be achieved *in vivo*, and the currently available methods are unlikely to be helpful in clinical decision-making. Nevertheless, these standardized tests are very valuable for research purposes and are helpful tools in the process of regulatory approval of novel products with anti-biofilm claims. In this presentation I will discuss the value of standardization and use of uniform technology in biofilm research, both from the point of view of the clinician and the point of view of the product developer. I will also spend some time discussing the point of view of European regulatory authorities (or the lack thereof) concerning standardization of anti-biofilm testing.

Anti-Biofilm Technologies: Pathways to Product
February 7, 2018 AGENDA

Hilton Crystal City at Washington Reagan National Airport, Arlington, VA

Time	Title	Speaker
7:15 a.m.–8:00 a.m.	Registration, Commonwealth Foyer, Lower Level Continental breakfast, Crystal Ballroom, Plaza Level	
8:00 a.m.–8:10 a.m.	Welcome and opening remarks Williamsburg/Yorktown Ballrooms, Lower Level	Paul Sturman, CBE Industrial Coordinator Laura Wahlen, CBE IA Program Chair; Research Assoc. III, Baxter Healthcare
8:10 a.m.–8:15 a.m.	SESSION 1: Medical Device Technologies Session Introduction, Garth James	
8:15 a.m.–8:45 a.m.	What can we learn about medical device associated infection pathogenesis from skin explant models?	K. Scott Phillips, Senior Biofilms Research Group Leader, Office of Science & Eng. Labs, Ctr. for Devices & Radiological Health, FDA
8:45 a.m.–9:15 a.m.	Bad to the bone: Antimicrobial devices in surgical infection and needed standards	Kenneth Urish, MD, PhD, Director, Arthritis and Arthroplasty Design Lab, Dept. of Orthopaedic Surgery, University of Pittsburgh
9:15 a.m.–9:45 a.m.	Antibiotic resistance and biofilm: An overview of research at the FDA Center for Drug Evaluation and Research Division of Applied Regulatory Science	Rodney Rouse, DVM, Research Veterinary Medical Officer and Assoc. Division Director, Div. of Applied Regulatory Science, Ctr. for Drug Evaluation & Research, FDA
9:45 a.m.–10:15 a.m.	BREAK, Commonwealth Foyer, Lower Level	
10:15 a.m.–10:35 a.m.	Update on methods used to assess biofilm prevention on surface modified urinary catheters	Jennifer Summers, Masters Student, Chemical & Biological Eng., MSU, CBE
10:35 a.m.–11:05 a.m.	Animal model for testing anti-microbial and anti-thrombogenic effectiveness of vascular catheter technologies	Nisha Gupta, Manager, Technology Development, Vascular R&D, Teleflex, Inc.
11:05 a.m.–11:25 a.m.	In-vitro and ex-vivo analysis of vascular catheters for biofilm	Garth James, Assoc. Research Professor, Chemical & Biological Eng., MSU; CBE
11:25 a.m.–12:00 p.m.	Session 1 wrap up and panel discussion	
12:00 p.m.–1:00 p.m.	Networking Lunch, Crystal Ballroom, Plaza Level	
1:00 p.m.–1:10 p.m.	SESSION 2: Surface Disinfection Technologies Session Introduction, Darla Goeres	
1:10 p.m.–1:40 p.m.	What's next for biofilm standard methods?	Darla Goeres, Assoc. Research Professor, Chemical & Biological Eng., MSU, CBE
1:40 p.m.–2:10 p.m.	Translating bench science into policy: How to drive policy toward science and technology	Jennifer Buss, VP, Science and Technology Policy, Potomac Institute for Policy Studies
2:10 p.m.–2:40 p.m.	Biofilm claims on EPA-registered biocides—Opportunities for public health and industrial applications	Elaine Black, Principal Regulatory Specialist, Ecolab
2:40 p.m.–3:10 p.m.	BREAK, Commonwealth Foyer, Lower Level	
3:10 p.m.–3:40 p.m.	Navigating the regulatory landscape in bringing hygiene solutions to market	Jim Arbogast, Vice President, Hygiene Sciences & Public Health Information, GOJO Industries
3:40 p.m.–4:10 p.m.	Standardization and use of uniform terminology in biofilm research—A European perspective	Tom Coenye, Professor, Pharmaceutical Sciences, University of Ghent
4:10 p.m.–5:00 p.m.	Session 2 wrap up and panel discussion	