Chapter 2
Antimicrobial and Anti-Biofilm Medical Devices: Public Health and Regulatory Science Challenges

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2.1 Public Health Challenge

Healthcare associated infections (HAIs) are one of the top 10 causes of death in the United States (~100,000 deaths per year) [1, 2] and impose a significant financial burden ($28–45 billion in 2007) [3]. HAIs can happen anywhere in the continuum of settings where patients receive health care (e.g., long-term care, home care, ambulatory care) [4]. A subset of HAIs acquired in healthcare—with some estimates over 60% [5, 6]—are related to medical device use (MD-HAIs). In fact, three of the four HAIs that are “areas of focus” in the 2013 HHS National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination are MD-HAIs [7]. These are catheter-associated urinary tract infections (CAUTI), central line-associated bloodstream infections (CLABSI), and ventilator-associated pneumonia (VAP). The fourth HAI focus area, surgical site infections (SSI), also includes MD-HAIs such as prosthetic joint infection (PJI). These infections are called out because of their significant human and financial burden. CAUTIs cost the US healthcare system more than $2900 per episode, a total of $2.9 billion per year [8].
CLABSIs costing US healthcare $1.2 billion and are associated with 56,000 deaths/year [9, 10]. PJI results in a 5-year survival rate (~75%) [12] similar to that of myocardial infarction (72%) [13] or colon cancer (~ 65%) [14]. Finally, VAPs total more than 250,000 cases per year at a cost of more than $5,000 per case [15]. Although there are many more MD-HAIs than just the ones that were called out in the National Action Plan, the collective financial burden of just these MD-HAIs alone (>$6.3 billion/year) more than suffices to show that MD-HAIs are a public health challenge that needs to be addressed.

There are many more MD-HAIs, some with much higher infection rates than those discussed above. Due to the large range of device types, the relatively low infection rate associated with many devices, and the lack of diagnostics to study MD-HAI pathogenesis clinically, it is extremely challenging to accurately assess the overall public health impact of MD-HAIs. A few authors have undertaken the arduous task of trying to get a better estimate of the overall impact of MD-HAIs. A 2012 paper by Busscher et al. focused on the infection incidence for 20 types of medical devices [16] (Table 2.1). The devices were grouped by implant site, with most devices having about 1–10% infection incidence with the exception of urinary catheters (33%) and abdominal wall patches (up to 16%). Nearly all voice prosthesis will eventually fail due to leakage caused by biofilm buildup. Incidence alone doesn’t tell the full story of the impact of MD-HAIs. Another review paper in 2010 by Wolcott et al. provided economic costs and mortality for a subset of MD-HAIs.

<table>
<thead>
<tr>
<th>Tissue implant site</th>
<th>Implant or device</th>
<th>Infection incidence over lifetime (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>Catheter</td>
<td>33 (per week)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>Central venous catheter</td>
<td>2–10</td>
</tr>
<tr>
<td></td>
<td>Temporary pacemaker</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Short indwelling catheter</td>
<td>0–3</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis catheter</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Fixation pin or screw</td>
<td>5–10</td>
</tr>
<tr>
<td></td>
<td>Sutures</td>
<td>1–5</td>
</tr>
<tr>
<td></td>
<td>Voice prosthesis</td>
<td>25 (per month)</td>
</tr>
<tr>
<td></td>
<td>Dental implant</td>
<td>5–10</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Cardiac pacemaker</td>
<td>1–7</td>
</tr>
<tr>
<td></td>
<td>Penile prosthesis</td>
<td>2–5</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Mammary prosthesis</td>
<td>1–7</td>
</tr>
<tr>
<td></td>
<td>Abdominal wall patch</td>
<td>1–16</td>
</tr>
<tr>
<td></td>
<td>Intraocular lens</td>
<td>0.1</td>
</tr>
<tr>
<td>Eye</td>
<td>Contact lens</td>
<td>0.1–0.5</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>Prosthetic heart valve</td>
<td>1–3</td>
</tr>
<tr>
<td></td>
<td>Vascular graft</td>
<td>1.5</td>
</tr>
<tr>
<td>Bone</td>
<td>Prosthetic hip</td>
<td>2–4</td>
</tr>
<tr>
<td></td>
<td>Prosthetic knee</td>
<td>3–4</td>
</tr>
<tr>
<td></td>
<td>Tibial nail</td>
<td>1–7</td>
</tr>
</tbody>
</table>

Adapted from Ref. [16]
including urinary catheter infections, infected cardiovascular devices, contact lens associated keratitis, orthopedic device infections, and ventricular shunt infection [17]. The review summarized information from journal articles, US government agency reports, and professional societies. The total estimated annual deaths were 82,000, with direct costs of $18 billion. This impact is commensurate with the scale of many major diseases such as breast cancer ($16.5 billion in 2010) [18, 19] or colorectal cancer ($14 billion) [19, 20].

The incidence and impact of MD-HAIs depend on numerous factors (e.g., the type of device material, the anatomic location, the use of prophylactic antibiotics) and are extremely diverse in terms of the microbes involved, the morbidity, mortality, chronicity, and treatment modalities. A major area of research in MD-HAI pathogenesis is the increasingly well understood role of biofilm [21] [23]. Biofilm is defined as self-assembling multicellular communities that behave differently from their free floating (planktonic) counterparts [22]. The number of microbes required to initiate biofilm formation on a medical device surface can be as low as 100 [23]. Normally the microbes must adhere to the exposed surfaces of a device long enough to become irreversibly attached to form a conditioning film. This largely depends on the device surface properties and the aqueous environment [24]. In recent years, there is an increasing understanding of how colonization and biofilm may play a role in the pathogenesis of medical device associated infections [25, 26] as well as development of drug resistant microbes [27, 28].

Device colonization and biofilm have unique clinical features such as persistence that make them challenging to address. This challenge requires a coordinated response from medical device manufacturers, clinicians and public health/regulatory authorities. Many efforts have been made to prevent HAIs at the first line of defense: hygiene and sterility. These include, for example, handwashing, facility cleaning and decontamination, and efforts to ensure a sterile surgical field. Despite the tremendous impact that these efforts have had in reducing the incidence of HAIs, there are still significant human and financial costs associated with MD-HAIs. Thus, it is not surprising that researchers and medical device companies are interested in developing antimicrobial technologies to prevent MD-HAIs [5, 29]. Because of the potential for colonization and biofilm to lead to MD-HAIs, many antimicrobial technologies employed on medical devices are specifically targeted to this aspect of microbial life.

In this chapter, we introduce the regulatory science of antimicrobial and anti-biofilm technologies designed to prevent MD-HAIs. In the United States, regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products [30]. Although the focus of regulatory science is not the invention of new medical products or technologies, in the total product life cycle (TPLC) of a medical device, the role of regulatory science can be very important. Good regulatory science can facilitate consumer access to innovative medical products that are safe and effective. In Section II, we first take a broad view beyond antimicrobial coatings to consider the range of possible medical therapies (e.g., device coatings, antimicrobials, vaccines) to prevent MD-HAIs, their use, limitations and safety. In Section III, we discuss regulatory definitions of the different types of technology and discuss mechanisms
of action and the importance of understanding combination products. Then in Section IV, we focus specifically on the regulatory science of antimicrobial technologies for medical devices. We show how the paradigm shift from a planktonic model of microbial life to a biofilm model introduces significant challenges to the scientific assessment process.

2.2 Antimicrobial/Anti-Biofilm Technologies to Prevent MD-HAIs

As discussed in Sect. 2.1, strategies to prevent MD-HAIs include antimicrobial and anti-biofilm technologies. Anti-biofilm technologies are differentiated from conventional antimicrobial strategies in that they are designed to target biofilm aspects of microbial life. They can be “enhanced” versions of antimicrobials that better penetrate biofilm or kill organisms in biofilm; whereas others may not even be lethal to organisms but may prevent colonization through a number of physical or chemical approaches. Conventional antibiotics or antimicrobials may also become anti-biofilm when they are released from a device surface to prevent colonization. A promising—but more challenging approach—is the development of technologies that are both biocompatible and encouraging to host integration while simultaneously resisting harmful bacterial colonization [31]. While these goals have been the source of much research progress over the past few decades, device coatings are not the only medical intervention to address MD-HAIs. Other types of technologies include vaccines, physical strategies for preventing or removing biofilm, and combinations of various modalities. Table 2.2 summarizes examples, effects and limitations of these technologies. It is separated into four major categories: (1) coating technologies/antimicrobials, (2) vaccines, (3) biofilm removal and (4) combined modalities. Systemic antimicrobials are beyond the scope of this discussion. Finally, although we don’t address them in this chapter, it is important to mention the increasing interest in the use of probiotic, “beneficial colonization” strategies which might compete with harmful bacteria [32, 33]. Although this work is still nascent, it may be recognized in the near future as a type of strategy to prevent MD-HAIs in some cases.

2.2.1 Antimicrobial/Anti-Biofilm Coatings

Coatings are one of the most common types of antimicrobial medical device technologies seen in the research literature. There are a number of types of coating strategies (as described below) and the diversity of strategies continues to increase as creative new technologies are developed.

Anti-adhesive Anti-adhesive coatings are designed to prevent the first stage in biofilm formation, colonization, eliminating the threat at the outset. Bacteria can adhere
<table>
<thead>
<tr>
<th>Anti-biofilm technologies</th>
<th>Examples</th>
<th>Mechanisms</th>
<th>Limitations</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coatings</td>
<td>Anti-adhesive</td>
<td>PEO, zwitterionic polymer, topographical structure, superhydrophobic coating</td>
<td>Low surface energy chemistry and nano-/micro-textured morphology reduce fouling, passive repelling</td>
<td>Stability, oxidation damage, in vivo efficacy may vary</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial loaded</td>
<td>Materials loaded with small molecule biocides, heavy metal, antibiotics, etc.</td>
<td>Active inhibition at the surface</td>
<td>Issues with optimizing release for effectiveness in preventing resistance, in vivo efficacy</td>
</tr>
<tr>
<td></td>
<td>Controlled/active release</td>
<td>Temperature-responsive copolymer, hydrolytically degradable film, pH-sensitive releasing</td>
<td>Active inhibition, release in response to stimuli</td>
<td>Release profile, stability, in vivo efficacy</td>
</tr>
<tr>
<td></td>
<td>Dual/multifunctional</td>
<td>Differentially adhesive surfaces, low fouling, and antibacterial coating</td>
<td>Prevent colonization while promote tissue integration, combines modalities to reinforce efficacy</td>
<td>Complex to optimize</td>
</tr>
<tr>
<td>Antimicrobial/anti-biofilm agents</td>
<td>Antibiotics</td>
<td>Gentamicin, rifampicin, minocycline, doxycycline, etc.</td>
<td>Bactericidal through multiple genetic and biochemical pathways</td>
<td>Resistance</td>
</tr>
<tr>
<td></td>
<td>Metal ions, oxides, nanoparticles</td>
<td>Silver zeolite, copper oxide, zinc oxide, ferric ammonium citrate</td>
<td>Release metal ions that target bacterial cells, some actions not well understood</td>
<td>Allergy</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Anti-biofilm technologies</th>
<th>Examples</th>
<th>Mechanisms</th>
<th>Limitations</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cationic compounds</td>
<td>Cationic surfactant, polymers, peptides, lipids, etc.</td>
<td>Disrupting bacterial membranes, allowing the free exchange of intra- and extracellular ions</td>
<td>Complex process in extraction, isolation and purification, expensive</td>
<td>[73–86]</td>
</tr>
<tr>
<td>Quorum sensing inhibitors (QSI)</td>
<td>Triazolyldihydrofuranone, cinnamaldehyde, hamamelitannin</td>
<td>Inhibit virulence factors and biofilm formation</td>
<td>New entities chemical, limited information</td>
<td>[87–93]</td>
</tr>
<tr>
<td>Dispersing enzymes</td>
<td>DNase I, DspB, α-amylase, restriction endonucleases</td>
<td>Cause biofilm detaching</td>
<td>expensive</td>
<td>[94, 95]</td>
</tr>
<tr>
<td>Bacteriophage</td>
<td>Caudovirales, ligamenvirales, some unassigned viruses</td>
<td>Viruses that infect bacterial cells</td>
<td>Host specified, purification</td>
<td>[96–99]</td>
</tr>
<tr>
<td>Natural compounds</td>
<td>Phenol, phenolic compounds, etc.</td>
<td>Diverse, not well studied</td>
<td>Complex composition add difficulties to optimize efficacy</td>
<td>[100] [101]</td>
</tr>
<tr>
<td>Biofilm removal techniques/physical strategies</td>
<td>Manual debridement, pulsed electrical fields, ultrasound therapy, and other topical and combination therapies</td>
<td>Remove multispecies bioburden or devitalized host tissue</td>
<td>Promising yet the efficacy has yet to be proven in the clinic</td>
<td>[102–106]</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Live, attenuated; toxoid; killed, whole cell; polysaccharide; polysaccharide—protein conjugate</td>
<td>Leveraging immune system</td>
<td>Critical phenotypes and factors are not adequately addressed</td>
<td>[107, 108]</td>
</tr>
<tr>
<td>Combined Modalities</td>
<td>Polyphenolic compounds and antimicrobial agent, enzyme-based compounds combined with metal ions, antimicrobials with non-contact ultrasound therapy</td>
<td>Synergistic antibacterial mechanism</td>
<td>Complexity</td>
<td>[104, 109–114]</td>
</tr>
</tbody>
</table>
and grow on natural and synthetic surfaces in an aqueous environment. Both specific and non-specific interactions play important roles in the bacterial adhesion and biofouling [34]. Biofouling in the context of medical devices includes non-specific adsorption of biological molecules that happens at the moment that a medical device comes into contact with biological fluids. Many anti-adhesive coatings, such as polyethylene oxide (PEO) and zwitterionic polymers, draw on the substantial body of literature on coatings designed to prevent biofouling [35–37]. More recent developments in superhydrophobic coatings have also been employed to reduce microbial adhesion[38]. In addition to these chemical strategies, a number of physical strategies also exist [39–41]. Fabrication of coatings with nano and micro-textured morphologies has been optimized at length scales that can discourage microbial adhesion [40, 42]. For all types of anti-adhesive coatings, an important limitation is the impact of biofouling on coating effectiveness. Nearly all devices are subject to biofouling by body fluids as well as elements of the foreign body response. In situations with large numbers of microorganisms and relatively static fluid dynamics, biofilm can form on surrounding surfaces first and then cover the coating. For anti-adhesive coatings that work through chemical means, stability is another key challenge. For these reasons, anti-adhesive coatings are often not regarded to be as effective as active coatings in vivo. In general, covalent coatings with a history of biocompatibility are seen as less of a challenge for safety testing than novel materials or eluting coatings [43]. Nanostructured materials, fundamentally different in their biological interactions than nanoparticles, can significantly change cell morphologies that direct their differentiation and survival [44]. Recent work by Kumar et al. has elucidated how a nanofibrous structured surface can change cell behavior through the control of cell shape [44]. Properties such as this may result in grouping of nanostructured surfaces with nanoparticles as an area of concern [45].

*Antimicrobial Loaded and Active/Controlled Release* The most common type of coating is antimicrobial loaded. Numerous types of antimicrobials have been loaded into polymer and hydrogel coatings [46–49]. The coating material is tuned to release these antimicrobials at varying rates, depending on the application. Controlling and ensuring reproducible release rates is one of the limitations of these types of coatings, and can result in significant differences in outcomes of performance testing. As a result, more sophisticated controlled/active release coatings have been developed to respond to signals such as temperature, pH or other changes caused by the presence of microorganisms[50–52]. The ultimate goal of this technology is to release antimicrobials only when microorganisms are present. Two key benefits to active release are (1) preserving the antimicrobial until needed, and (2) reducing the potential for development of resistant organisms.

*Multifunctional* Multifunctional coatings, still in the early stages of development, are designed to combine any of the above concepts and may also combine host cell integration with antimicrobial function [53–55]. These coatings are especially promising for applications where an implant requires successful integration with host tissue to achieve the best long-term functionality. The added complexity of these products can make their safety profile more challenging to predict.
2.2.2 Antimicrobial Agents Included in Anti-Biofilm Strategies

Most of the antimicrobial agents that have been used in legally marketed medical device–drug combination products—such as antibiotics and metal ions—already have a long history of use against planktonic organisms.

Antibiotics Some of the antibiotics used on devices include gentamicin, tobramycin, rifampicin, and clindamycin [56–58]. Antibiotic resistance is an important concern with many of these agents. For example, bacteria on gentamicin-loaded bone cement in vivo have been found to have gentamicin resistance [59]. Further research needs to be conducted with the goal of learning how these coatings should be used in view of good stewardship principles. The Infectious Disease Society of America (IDSA) states that antimicrobial stewardship is the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. “Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains” [60].

Metals Silver is the most commonly used metal seen in antimicrobial coatings. Minimum inhibition concentration (MIC) testing has shown a high level of silver antimicrobial activity in vitro [61, 62]. Some silver-coated dressing products have also shown rapid bactericidal action and can achieve a five-log reduction in a comparatively short time [63]. Other metals have been used but suffer from toxicity limitations at higher concentrations [64]. A combination of metals has sometimes been employed [65]. There are numerous reviews on silver-containing medical devices [67–71]. Current in vitro tests for performance of silver-containing coating technologies are not always good predictors of how they will perform in vivo [67, 68]. The outcome of these studies depends on the type of device, the specific use of the device, the type of silver coating, and the test conditions. The “apparent” performance of silver-containing products depends on the test methods employed [69]. Silver is one of the few antimicrobial technologies on medical devices that have been the subject of multiple clinical trials. The outcomes of these trials depend on factors such as duration of use, patients, bacterial species present, materials, and catheter care mistakes [70, 75–77]. An important consideration is the form of silver, i.e., as a salt or as a nanoparticle. Although there was initially very little information on the safety of nano-silver vs. ionic silver, significant research in the area of toxicology/biocompatibility has helped clarify how risk assessment might be performed [72].

Cationics Another group of conventional antimicrobial agents that have been researched and/or employed in device coatings is cationics, including quaternary ammonium compounds (QAC) [73], antimicrobial peptides (AMPs) [74], chlorhexidine [75], poly(hexamethylene biguanide) (PHMB) [76, 77], and chitosan [78, 79]. Antimicrobial peptides (AMPs) are found in a variety of organisms as a native defense against bacteria and are the source of inspiration for synthetic versions with higher efficacy [79, 80]. A common strategy for implementing AMPs involves sur-
face functionalization with a heterobifunctional cross-linker [81]. Compared with other cationic compounds such as PHMB, comparatively higher concentrations of these biocides are needed for efficacy and lasting biofilm inhibitory effect, which may lead to potential bacterial resistance [82, 83]. A number of studies show that cationics, especially PHMB, have a favorable toxicity profile with regard to skin irritancy and hypersensitivity at typical topical use levels [84, 85].

Many antimicrobials still in the research and development phase are specifically targeted to medical biofilms:

**Quorum Sensing Inhibitors** One of the earliest concepts to be tested was based on inhibition of “quorum sensing.” Bacteria colonizing materials communicate when they reach a critical mass using small molecules called quorum sensing molecules, which can regulate biofilm formation and virulence factor secretion [92–94]. Both in vitro and in vivo tests showed that quorum sensing inhibitors could shut down this communication process and thereby prevent biofilm formation and infections associated with antibiotic-resistant strains [87, 88]. It has been proposed in the literature to use these agents on medical devices in combination with conventional antimicrobials, to reduce biofilm formation and thereby enable antimicrobials to work more effectively [28]. Since most of these inhibitors are small molecules, cytotoxicity is often a safety concern [89]. Because inhibitors are not lethal to microorganisms, it is sometimes proposed that “resistance” can’t develop over time [90, 91]. However, this theory is controversial as it is not known if there are other factors that would give resistant clones a selective population advantage over longer periods of time. Quorum sensing inhibitors have been proposed for use in direct application to a colonized surface or as part of device coatings [92, 93].

**Dispersing Enzymes** Another approach is to remove biofilm after it is formed using dispersing enzymes. A number of enzymes are specifically targeted toward breaking down the molecular cross-linking found in biofilm matrices. Because these enzymes are naturally derived, they are relatively expensive to produce [94]. Although the enzymes are very effective at detaching many biofilms, an important safety concern is that the detached bacteria may travel to distant sites and reinitiate colonization, causing satellite infections [95].

**Bacteriophage** Bacteriophage is a naturally sourced antimicrobial that can be specifically strain targeted [96]. Minimal impact on nontarget bacteria or tissues was reported [97]. The immune system may inactivate phage in vivo [98]. While bacterial resistance to phage is possible, a growing number of engineered phages are emerging to provide alternatives [99].

**Natural Compounds** A number of natural small molecules have been isolated from plants that might be used in, on, or in conjunction with medical devices. These may be compounds under investigation for other properties, which are discovered to have antimicrobial function. Some of them may have beneficial “probiotic” effects by favoring commensal colonizers while being harmful to more virulent organisms [100, 101].
2.2.3 Biofilm Removal

Manual debridement is the centuries old technique for biofilm in accessible superficial wounds. It is considered a very effective way of managing the biofilm in chronic wounds by transforming “non-healable” wounds to healable wounds [102]. Because many medical device surfaces are inaccessible and can’t easily be removed/cleaned without additional surgery, one focus of removal has been to use long-range physical methods such as ultrasound therapy [103]. Another potential approach for partially accessible devices is application of pulsed electric field with or without combined antibiotic therapy [112–114]. Electric fields have been applied (or generated through redox reactions) to interfere with important electrostatic factors in adhesion. A potential safety concern with physical removal methods is that biofilm clusters containing bacteria and endotoxins from physical removal procedures can migrate to other locations in a wound or become systemic, potentially resulting in life-threatening sepsis [105]. Another concern is to ensure safe use of electric fields, given the low threshold for tissue damage. More development is needed to translate this technology for the clinic [103].

2.2.4 Vaccines

More recently, vaccination and immunization have been explored with specific focus on effectiveness for preventing medical device-associated infection [106]. Specifically, prevention of prosthetic joint infection (PJI) associated with \textit{S. aureus} infection has been targeted through the use of preoperative passive immunization with neutralizing antibodies. Vaccines have also been developed specifically to target upregulated antigens found in biofilm [107, 108]. A multivalent vaccine combining antigens upregulated in the biofilm and planktonic forms of \textit{S. aureus} has shown efficacy in an animal model of infection without the use of antibiotic therapy. In the future, vaccines may play an important role in helping prevent device-associated infections without inducing drug resistance. However, it would be premature to assume that these technologies will be successful before their safety and effectiveness are successfully demonstrated in human clinical trials.

2.2.5 Combined Modalities

Combination therapy has been successful in other areas of medicine (HIV, cancer) because of the ability to target multiple biological mechanisms, thereby preventing a resistant population from emerging [109, 110]. In a similar manner, it may play an important role in fighting device-associated infections successfully due to the benefits of diverse modes of action and improvements in preventing development of microbial resistance. Many antimicrobial agents have been combined with other
antimicrobials to increase efficacy. For example, polyphenolic compounds have been combined with antibiotic and calcium modulators for acute pneumonia infection in vitro [111], enzymatic removal has been combined with metal ions [112], electrical fields have been combined with antimicrobials, and ultrasound has been combined with antibiotic therapy [113, 114].

2.3 Types of Antimicrobial/Anti-Biofilm Technologies: Device, Drug, Biologic, and Combination Products

Anti-biofilm technologies for medical applications such as those described above may be drugs, devices, biological products, or any combination of two or more of the above (combination product). Therefore it is helpful to review the definitions of these terms:

**Drug** (FD&C Act, 21 U.S.C. § 321(g)):
The term “drug” means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C) [115].

**Device** (FD&C Act, 21 U.S.C. § 321(h)):
The term “device” (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes [115].

**Biological Product** (PHS Act, 42 U.S.C. 262):
The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings (Public Health Service Act Sec. 351(i)).
Combination Product (21 CFR 3.2(e)):

The term combination product includes:

1. **A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity**;
2. **Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products**;
3. **A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or**
4. **Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.**

Many devices which incorporate antimicrobial technologies have been determined to be combination products. A combination product is assigned to an agency center or alternative organizational component that will have primary jurisdiction for its premarket review and regulation. Under section 503(g)(1) of the Act, assignment to a center with primary jurisdiction, or a lead center, is based on a determination of the “primary mode of action” (PMOA) of the combination product. For example, if the PMOA of a device–biological combination product is attributable to the biological product, the agency component responsible for premarket review of that biological product would have primary jurisdiction for the combination product. A final rule defining the primary mode of action of a combination product was published in the August 25, 2005, Federal Register. The final rule defines primary mode of action as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.” In some cases, neither the FDA nor the sponsor can determine the most important therapeutic action at the time a request is submitted. A combination product may also have two independent modes of action, neither of which is subordinate to the other. To resolve these types of questions, the final rule describes an algorithm FDA will follow to determine the center assignment. The algorithm directs a center assignment based on consistency with other combination products raising similar types of safety and effectiveness questions, or to the center with the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product. The final rule is effective November 23, 2005 [116] (Fig. 2.1).

The classification of the anti-biofilm technology, as a device, drug, biological product, or a combination product, and the lead center assignment govern the regulatory requirements for the product. Information on the resources for medical devices can be found at: [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115879.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115879.htm) [118].
Information on the resources for drugs can be found at: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm238040.htm [119]. Resources for biological products can be found at: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm2005991.htm

FDA maintains a public database of products cleared through the 510(k) premarket notification pathway (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfmg) [120]. This database can be used to search for examples of antimicrobial/anti-biofilm technologies. It may be helpful to limit the scope of products searched by searching using a three-letter product code (procode) which is specific to a device type. If you don’t know the procode for a device type, you can search for it here: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm. It is prudent to understand the regulatory process which would apply to a specific product type and to obtain early feedback, when necessary, through appropriate pre-submission programs. For medical devices, the Center for Devices and Radiological Health (CDRH) Division of Industry and Consumer Education (DICE) has an email response form online for assistance, available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactDivisionofIndustryandConsumerEducation/default.htm.

2.4 Regulatory Science Challenges of Antimicrobial/Anti-Biofilm Technologies in Medical Devices and Combination Products

2.4.1 Paradigm Shift

To better understand the challenges associated with the regulatory science of biofilms and anti-biofilm technology, it is important to consider the paradigm shift in microbiology from a planktonic to biofilm understanding of microorganisms, in particular bacterial and fungal organisms that are among the key causative agents of MD-HAIs. Until the late twentieth century, wound care (wound debridement) and dental applications (plaque) were the primary medical areas where biofilm was
studied, due to it being visibly present as a persistent source of infection and inflammation. The increase in biofilm publications (Fig. 2.2) shows how in the 1990’s work began to show a paradigm shift. Between 2006 and 2015, publications on biofilms nearly quadrupled, reflecting increasingly widespread interest.

Many classic microbiological studies relied heavily upon the study of planktonic cells because of the capability and convenience to perform experiments with suspended bacterial culture. As microbiologists realized that the majority of microbes on earth are found in structured biofilm ecosystems and not in the planktonic form [121], they began to realize the importance of biofilm in the etiology of device-associated infections. In colonized medical devices, bacterial life is a dynamic process in which cells grow in biofilm and may be shed into the environment to colonize other surfaces downstream of the first. Biofilm formation on medical devices comprises a number of physical, biological, and chemical processes—protein fouling, macromolecule adsorption and transportation, cell–material interaction, quorum sensing, and interaction with mammalian cells and immune system. It is important to understand the total process as well as the relationships between each stage of the cycle. Each stage in this process has a unique potential to play a role in medical device failure or patient harm [5].

The composition of biofilm is significantly different from planktonic organisms and may exacerbate the ability of a microbe to cause device failure and patient harm. The extracellular matrix (ECM) is composed of polysaccharides, proteins, nucleic acids, and other biomolecules. Water (97%), ions, soluble low- and high-molecular mass products, and cells are trapped in this matrix [122]. In addition to the physical and chemical protection afforded to cells living in biofilm, the potential for emergence of drug-resistant organisms may also be increased. The close association of bacteria in biofilms increases the potential for sharing genetic information that encodes for antimicrobial resistance. Even the structure of multi-species biofilms seems to be optimized for synergistic metabolism [123]. Bacteria living in a thick biofilm have a reduced metabolic rate (long stationary phase), which reduces the effectiveness of common antibiotic mechanisms and enables persister cells.

![Fig. 2.2 The number of scientific publications per year with topic of “biofilm” (Web of Science, accessed 04/30/2015)](image-url)
As our understanding of the importance of biofilm has increased, there is now a shift to studying how biofilm affects the clinical path of infections [28]. The role of biofilm in medical device-associated infections is difficult to study in vivo because it is microscopic and internalized. Non-specific inflammatory markers cannot distinguish between infections caused by planktonic cells and biofilm infections [124, 125]. Explants [130] of samples are difficult to study and may have false negative or false positive results [126]. In the past, swabs and samples that yielded negative results were considered clean. But now we are learning that these techniques do not always detect biofilm colonization which can cause long-term low-level sequelae [127]. Colonized devices do not always meet the definition of “infection” because they don’t have the clinical signs and symptoms of an infection [128]. Yet studies are increasingly showing examples of how the presence of biofilm may impact aspects of device function directly (such as by blockage) or indirectly (by secondary interactions such as inflammatory processes). Chronic, subclinical infection due to biofilm has also been suggested as playing a possible role in changes to the immune system [136–139].

A lot of the information that we have on biofilm comes from the areas of wound care, where biofilm is externalized, as well as from studies of explanted devices and anecdotal reports of biofilm observed in surgery. We also see the inevitable development of biofilm in indwelling devices such as urinary catheters and endotracheal tubes. Despite the difficulty of detecting and measuring biofilm on many implanted devices, what we do know from clinical treatment of external biofilms (e.g., diabetic foot ulcers) is that they are extremely resistant to drugs and even physical removal and present an expensive and protracted battle that is often life-threatening for those with comorbidities. This paradigm shift in the understanding of biofilm’s clinical role portends a need to think differently about the role of antimicrobial/anti-biofilm technologies in medical devices.

2.4.2 Impact of Paradigm Shift on Regulatory Science

The biofilm paradigm shift may have implications for medical device safety and performance. However, this shift is only now being integrated into microbiological studies in general. Some of the areas in biofilms and anti-biofilm technologies such as antimicrobial coatings needing further scientific research and development are discussed below.

2.4.2.1 Standardized Terminology

The definitions and claims involved in biofilms and anti-biofilm technology need to be generally agreed upon by all of the parties involved—industry, regulators, trade groups, and standards groups. Biofilm, from the very beginning, is more challenging to define than planktonic life because of the dynamic process that the term represents. The late Dr. Bill Costerton, one of the pioneers of biofilm research, defines
biofilms in *The Biofilm Primer* as “self-assembling multicellular communities that behave differently from their free floating (planktonic) counterparts” [22]. While this captures one stage of the biofilm life cycle, other stages such as adhesion, colonization, and dispersion are also an important part of the process. Many questions need to be clarified in the change from a planktonic to biofilm paradigm. For the purpose of quantifying antimicrobial effectiveness, planktonic microbiology was mainly concerned with counting bacteria and log reductions. The dynamic biofilm life cycle introduces nuanced and complex interrelated phenomena that challenge conventional scientific understanding. For example, when does adhesion become colonization? When does colonization become biofilm? What does it mean to “eradicate” biofilm—is it removing just the bacteria, part of the ECM or all traces of organic material? Metrics (e.g., how long, how many, how much) need to be developed for many of the terms surrounding medical device biofilms.

### 2.4.2.2 Performance Goals

It is important to understand what performance goals are associated with anti-biofilm technologies. Performance testing of planktonic-targeted antimicrobials typically involves minimal inhibitory concentration (MIC) or log reduction of colony forming units. But there are additional goals that have been targeted for anti-biofilm medical device technologies. Some examples of goals noted in the literature are:

- “inhibit bacterial adhesion/colonization” [36, 138]
- “prevent biofilm formation” [129]
- “control of bacterial biofilm growth” [130]
- “penetrate and kill bacteria in the biofilm” [131]
- “reduce biofilm viability” [114]
- “degradation of biofilm matrix components” [132]
- “removing medically important biofilms” [133]

We have underlined the main action verb in each of these statements because they are ordered from early stage (inhibition) to post-biofilm formation (removal). This shows how the dynamic life cycle of bacteria becomes much more important in performance goals associated with biofilms vs. goals associated with planktonic bacteria. There are still many questions associated with understanding these goals. The tremendous diversity of anatomic locations and uses of medical products means that the claims may not be “one size fits all.” For example, what if an anti-biofilm technology on a long-term catheter can reduce biofilm over very short time periods (hours) but makes little difference in the infection incidence over the total period of device use (weeks)? Or what if an anti-biofilm technology works well to prevent biofilm in a wound dressing, but not on a urinary catheter? In some cases, there are questions about whether achieving the performance indicated by the claim may undermine the overall performance or safety of the product. For example, what if an antimicrobial coating on a material placed in the oral environment kills harmful bacteria but also kills commensal, nonpathogenic organisms that would normally
colonize surfaces and protect the host? Or what if an antimicrobial coating on an orthopedic implant leads to development of drug-resistant organisms?

2.4.2.3 Antimicrobial Mechanisms

With planktonic cells, there is usually significant literature evidence for how antimicrobials exert their effects (such as through receptor–ligand interactions, cell membrane disruption, etc.). However, for anti-biofilm technologies, the mechanism of how a technology works at the molecular scale may span scientific disciplines, making it challenging to study and understand. This is complicated by the fact that many anti-biofilm technologies may also be multimodal, meaning that they exert chemical and/or mechanical action in more than one modality. An example might be an anti-adhesion strategy that is also toxic to bacteria. Experiments examining only adhesion may not take into account the significant effect of bacterial toxicity. As a result, experimental studies of anti-biofilm technologies need to be carefully designed to ensure that they consider multimodal antimicrobial mechanisms. If there is more than one possible modality, they should be carefully controlled to account for confounding variables from the alternate modality.

Because of the potential for anti-biofilm technologies to be multimodal, it is also important to understand how a particular technology leads to a specific performance goal. An example given at a recent workshop illustrated this principle. The specific example involved wound dressing with a silver coating: If the dressing serves as a wound covering and the silver helps prevent bacterial colonization within the wound dressing, the wound dressing is a combination product with a medical device PMOA. If the same product serves to treat an infected wound, it is a combination product with a drug PMOA (Fig. 2.1) [134].

2.4.2.4 Antimicrobial/Anti-Biofilm Test Methods

In Vitro

Test methods found in voluntary consensus standards (not necessarily recognized by FDA) related to antimicrobial technologies fall into the two major categories of either conventional antimicrobial performance (planktonic) or anti-biofilm performance (Table 2.3).

Test methods for planktonic performance are mature and highly differentiated. Often an antimicrobial preservative may be included as part of a medical device material or formulation. The USP 51 preservative test measures the amount of bacterial growth in planktonic solution. Thus, it can be used to measure inhibition of microbial growth in a product. The test is most relevant for testing of unused solutions to show that they remain sterile before use. The Kirby–Bauer test (zone of inhibition, ZOI) is a rapid and simple way to evaluate susceptibility of a specific organism to an antimicrobial [135]. This format is more often used to help guide
decision making on therapeutic treatment or in research for rapid screening of potential antimicrobial chemistries. The agar diffusion assay is not necessarily indicative of the effectiveness of an antimicrobial strategy against colonization or biofilm. Another test often used to show antimicrobial susceptibility is MIC testing. Because of the widespread use of this test, it is good for comparing potential antimicrobials in terms of understanding the minimum concentration needed to have an effect. Both ZOI and MIC tests may not be as relevant when an antimicrobial is used in the context of biofilm. These assays were not designed to be used for testing anti-biofilm strategies, but are often used in the literature to assess novel anti-biofilm technology.

There are a number of ASTM standards specifically dealing with biofilm that are sometimes used in the literature to evaluate anti-biofilm technologies for medical devices [136–138]. These assays were mostly developed for the assessment of environmental cleaners and other nonmedical technologies. While these standards may be a good starting point for development of appropriate test methods, in most cases they lack correlation with in vivo outcomes. The endpoint measured in biofilm assays is also an important consideration. The endpoints used in many biofilm assays often have limited correspondence with in vivo performance. Biofilm test standards are usually in the biofilm reactor format or biofilm assay format. Reactor standards tend to focus more on the reproducible creation of a biofilm. These tests

### Table 2.3 Standard test methods for antimicrobial performance

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Test method/Reactor platform</th>
<th>Measurement process</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planktonic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLSI M02-A11</td>
<td>Antibacterial disk susceptibility</td>
<td>Measure zone of inhibition</td>
<td>Not appropriate for coating performance, doesn’t test biofilm</td>
</tr>
<tr>
<td>USP 51</td>
<td>Preservative</td>
<td>Plating directly</td>
<td>Only measure bacteriostatic effectiveness in solution</td>
</tr>
<tr>
<td>CLSI M07-A9</td>
<td>Antibacterial susceptibility</td>
<td>Plating directly</td>
<td>Doesn’t test biofilm</td>
</tr>
<tr>
<td>Biofilm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTM E2196</td>
<td>Rotating disk</td>
<td>Plating from coupons</td>
<td>High variability</td>
</tr>
<tr>
<td>ASTM E2647</td>
<td>Drip flow reactor</td>
<td>Confocal microscopy or plating from coupons or direct coatings</td>
<td>Low throughput</td>
</tr>
<tr>
<td>ASTM E2562</td>
<td>CDC flow reactor</td>
<td>Plating from coupons</td>
<td>Large volumes</td>
</tr>
<tr>
<td>ASTM E2799</td>
<td>MBEC assay</td>
<td>Plating from plastic pegs</td>
<td>Mostly for liquids</td>
</tr>
<tr>
<td>ASTM VVk32449</td>
<td>Single tube assay</td>
<td>Plating directly</td>
<td>For liquid disinfectants only</td>
</tr>
</tbody>
</table>

The tests in this table are not necessarily recognized by FDA.
were developed as biofilm reactors and are not meant to simulate real-world in vivo use. Reactor standards often rely on plating and colony counting to evaluate results. While this is the gold standard for quantifying bioburden in planktonic solutions, it is more challenging and burdensome with biofilm. The process of recovering bacteria from biofilm on a surface may introduce error due to poor recovery or failure to grow after extraction. Biofilm assays are more suitable for measuring anti-biofilm performance but are often inappropriate for the context of medical device use. An ideal test method should reflect, first and foremost, how and where a product will be used. The type of microorganism(s), inoculum, composition of artificial soil, temperature, time of exposure, and endpoint measurement should be carefully designed and validated with matching in vivo or clinical data. It is important not to underestimate the impact that biofouling during actual device use might have on performance [139]. Anti-biofilm technologies that are covalently attached to a surface (non-eluting) may be rapidly passivated by proteins which then become a base for colonization. More challenging questions surround the effect of growth media on the test outcome. Although growth media have often been used to achieve reproducible and measurable results, in the real-world scenario, biofilm may have different persistence traits if it develops in different in vivo microenvironment with different types of nutrient sources. Many biofilm ecosystems also involve synergistic polymicrobial metabolism [140]. Testing a monoculture system may not adequately replicate these advantages. Questions have also been raised about differences in the biology (gene regulation and expression) in in vitro test environments versus in vivo [132]. Little has been done to understand how the phenotypic state of biofilm bacteria on a plastic surface in a microplate compares with a biofilm in vivo or even in an infected tissue (ex situ). Finally, the lack of immune response in test environments is a crucial missing link to understanding why some anti-biofilm technologies might be more effective than others in real-world use.

More realistic in vitro models are being developed and have great promise to improve on current tests. A porcine ex vivo model has been used to grow biofilms on the actual tissue that is similar to a wound, creating biofilm that is more robust than what is seen in current testing formats [141]. The model is used to test potential anti-biofilm strategies for infected wounds. When compared with biofilm on plastic plates, the model found that many effective anti-biofilm compounds in plastic plates were not effective to prevent biofilm in the ex vivo model. The results are currently being validated with an animal model. Another important step toward increasing clinical relevance is the use of co-culture models with human immune cells [141, 142]. While it is challenging to keep microbes and cells healthy in the same test environment, doing so can yield unique insights into how materials or solution components affect the ability of the immune system to clear microbial threats. A very different approach to improve reproducibility and throughput of anti-biofilm testing is the use of microfluidic devices [143, 144], including medical-device-on-a-chip (MDoC) [145, 146]. Ultimately, lab-on-a-chip technology may be able to provide a next-generation platform for a simulated test environment with numerous advantages over current strategies.
2.4.3 Animal Studies

Although we do not extensively review animal testing in this chapter, there is a substantial body of literature on animal biofilm models. Although many animal models are complicated by the same lack of biofilm specific diagnostics as clinical assessment, there are a number of promising test methods that take advantage of differences in scale for small animals to achieve real-time monitoring. One of these is OCT imaging that can quantify biofilm on an implanted device [147, 148]. The technique is promising for potential clinical use as well as on devices near the skin’s surface, such as breast implants and dermal fillers. Another promising strategy is the use of luminescence to monitor both the bacterial bioburden and the immune response to implants simultaneously in mice [149]. This technique has been used to study how anti-biofilm technology can potentially prevent colonization of implanted materials while retaining biocompatibility. The ability to use this model for extended periods of time (as long as 1 year) allows for potential studies of late-term infections and chronic biofilm that are not achievable with most models. There are also a number of large animal models which are thought to be more comparable with human outcomes due to anatomic and immune system similarities [150, 151].

2.4.4 Clinical Testing

There are an increasing number of studies that correlate in vivo and clinical outcomes with in vitro anti-biofilm testing. Entire books have been written about this burgeoning field, which is too large to discuss in detail in this chapter [6, 152, 153]. It is worth noting that most of these studies are relatively small, and the diversity of animals, tests, and anti-biofilm technologies tested makes it difficult to assemble sufficient metadata. These studies show that in some but not all cases, there is a clear correlation between in vitro testing and clinical outcomes. Typically the bioburden from an in vivo sample is used to compare with in vitro reductions in biofilm or organisms. A few studies have found correlations between in vitro reduction of bioburden and mortality or morbidity. Fully powered clinical trials with anti-biofilm technology are rarely achieved due to the small number of participants that can be enrolled. One strategy to get around this challenge might be to use data from the few clinical trials that have been done to back correlate with test methods being developed for anti-biofilm technology. Another strategy that has been suggested is to initially develop anti-biofilm technologies for revision surgery, where the percentage of device-associated infections is typically much higher. Once a strategy has shown benefit for revisions, it may be possible to collect clinical data over time to support more general use.
2.4.5 Questions About Safety: Antimicrobial Resistance and Biocompatibility/Toxicology

An important item often missing in current anti-biofilm technology testing relates to assessing new issues of safety related to these technologies. Drug resistance is one of the chief public health concerns of the twenty-first century [154]. It is not clear if the use of antimicrobials on medical devices, particularly where low concentrations may elute over time, has an impact on the emergence of antibiotic resistant bacteria. To our knowledge, no standard formats have been developed to study if concentration gradients found in these technologies can lead to resistance or cross-resistance. Another concern mentioned above is the preservation of native colonizing microbiota [155]. There is little to no information on how to assess anti-biofilm technology’s effect on commensal microbial communities. We know from the case with drug therapy’s effect on the healthy colonizers in the gut that altering the microbial ecosystem can have harmful effects on human health. Some researchers have even tried to turn this concern on its head by developing ways to colonize medical devices with healthy, non-virulent microbial strains—“probiotics” that help protect from colonization by pathogenic organisms [156]. Finally, as mentioned above, many anti-biofilm technologies involve new nanotechnology such as nanoparticles or nanotopology that has not been previously been used in the clinic.

2.5 Conclusions

The science of antimicrobial and anti-biofilm technologies on medical devices is a diverse, interdisciplinary field associated with increasing understanding of the role of biofilms in MD-HAI pathogenesis. The public health challenge presented by MD-HAIs is a key driving force for the need to continually improve the regulatory science associated with these technologies. Antimicrobial coatings and anti-biofilm technologies on medical devices in general are not the only weapon in the arsenal of modern medicine. Other technologies should be considered when more appropriate or when combinations can be employed with synergistic potential. Device design and instructions for use should be thoughtfully considered to minimize potential for contamination and biofilm. While there are many novel technologies with demonstrated potential in vitro, it is important to understand the use of these technologies in the context of achieving overall best clinical outcomes with minimal cost. Many of the current challenges in the regulatory science of antimicrobial technologies might be addressed through research on the pathogenesis of device associated infections. Two keys to this research are (1) improved diagnostic methods to identify and quantify biofilm and its role in infections and (2) further development of in vitro methods that are correlated with specific in vivo outcomes. It is important to think about antimicrobial technologies not only from the perspective of microbicidal properties but also their interaction with the host immune system, effect of medical device integration and function, and antimicrobial stewardship (i.e., contribution to or prevention of drug resistance) [157].
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