PROPOSAL

The Impact of Biofilm Regulatory Policy on the Development of Healthcare-Related Products

Submitted to:
Montana State University Proposed Center for Regulation and Applied Economic Analysis (CRAEA)

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November 15, 2016

Abstract

Bacterial infections associated with medical devices and hospital procedures account for an enormous and growing portion of heath care-related costs and patient mortality. Health care-associated infection (HAI) alone cost approximately $30 billion in potentially preventable expenditures annually. The US Department of Health and Human Services (HHS) has identified biofilms as an important etiological agent in HAI. The challenge of minimizing HAI involves not only employment of best practices by health care providers, but also the availability of products designed to prevent or mitigate HAI. Although US industry has responded to this challenge through the development of anti-biofilm products, there are concerns that prohibitively restrictive regulatory policies may inhibit anti-biofilm product development efforts. The proposed research aims to assess the impact of these regulatory policies through investigation of decision making at both health care companies developing anti-biofilm products as well as agencies regulating them (FDA and EPA).

Specific Aims

The principal aim of this work is to understand and report how regulatory policy at the national level influences decision making at healthcare-related businesses, specifically with regard to the development of products designed to prevent or mitigate HAI associated with biofilms. It is our hypothesis that an ambiguous and/or overly cautious regulatory climate inhibits innovation in this area. The rationale for this work is the current exorbitantly high cost of HAI, both in expenditures and human life, the fact that innovative technologies for biofilm control exist but have yet to be fully integrated into the health care product arsenal, and that the balance of risk vs safety that necessarily drives regulatory decision making may be too cautious in light of the magnitude of the HAI problem.

Significance

The treatment of HAI costs approximately $30 billion annually. More importantly, they cause significant human suffering and loss of life, resulting in an estimated 1.7 million infections and

approximately 100,000 associated deaths in the US annually (Klevens et al., 2002). Major causes of HAI include surgical site infection, central line-associated blood stream infection (CLABSI), ventilator-associated pneumonia, and catheter-associated urinary tract infection (CAUTI). These infections are caused by frank and opportunistic pathogenic bacteria such as *Staphylococcus aureus* and potentially many others. Best practices for any surgical procedure include the administration of antibiotic therapy both pre- and post-operatively, yet HAI occurs in approximately 5% of all hospitalized patients. A combination of factors have been postulated to be responsible for this, including potentially compromised immune systems in hospitalized patients, the presence of antibiotic resistant organisms in the hospital environment, and the growth of infection-causing organisms as biofilms. Bacteria grown in biofilms are well understood to be much more resistant to antibiotics than their free floating (planktonic) counterparts (Stewart and Costerton, 2001). Furthermore, examination of medical devices explanted from patients with persistent bacterial infections has confirmed the role of biofilms in these HAI (Costerton et al., 2004). The regulatory community recognizes that biofilms are important to HAI and that the link between biofilm and infection is not fully understood. In fact, biofilms mentioned numerous times as knowledge gap in National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination (US Department of Health and Human Services, 2013). Perhaps because of the incomplete understanding of biofilms as causative agents in persistent infection, the regulatory community (principally FDA), have been reluctant to promulgate regulations for medical devices intended to reduce, inhibit, or kill biofilms.

Bringing a new or innovative medical device to market is often an enormously expensive undertaking. The progression from basic research and development, to laboratory models, pre-clinical testing, and finally clinical testing can easily cost tens to over 100 million dollars. Furthermore, a recent study noted that new medical device submissions to FDA actually fell from 2002-2010 and concluded that this was a result of an ambiguous or unnecessarily burdensome regulatory process (Makower et al., 2010). FDA's role as protector of public health is not in question, however, it must also be noted that unnecessary delays or expense in bringing potentially life-saving products to market may be counterproductive to innovation and the adoption of new technologies. FDA's position is particularly problematic with regard to biofilms because of the failure to recognize persistent infection and surface associated bacterial growth as essentially biofilm problems.

This research will look specifically at medical devices intended to mitigate biofilm, either on the device itself or on tissue in contact with the device. It will seek to better understand the experiences of the regulated community (medical device manufacturers) and the extent to which a lack of clear FDA guidance on the approval process for biofilm-related devices has delayed or inhibited new product innovation. We anticipate that the results of this work can be used within the agency to better understand the implications of their current methods of review and develop a more efficient process going forward. This work will utilize undergraduate students and will broaden public understanding of the societal impacts of medical device regulation, both of which are central to CRAEA's mission.

Innovation

While the issue of FDA's regulatory impact on medical technology innovation has been investigated (Makower et al., 2010), there has been no focus specifically on biofilm-related product innovation. This is important because the majority of HAI are biofilm infections, and products intended to mitigate HAI must necessarily seek to kill or prevent biofilm. The proposed investigation will be a timely addition to the knowledge base Makower developed 6 years ago.

The Principal Investigators are uniquely qualified to understand and elucidate the regulatory climate and its impacts on biofilm-related health care product development. Dr. Sturman is the industrial coordinator at the Center for Biofilm Engineering (CBE) at Montana State, and has developed contacts at numerous medical device manufacturers through the CBE's Industrial Associates Program. Furthermore, Dr. Sturman has worked closely with FDA over the past 4 years to develop an annual "Anti-Biofilm Technologies" conference, held in the Washington DC area each February. These interactions will greatly assist information gathering efforts as part of this project. Drs. Sturman and Kerins have also previously collaborated on a Biofilm Market Survey funded by the MSU Research Expansion Fund. This work identified many potential biofilm-related markets, with HAI-related products identified as a prominent growth area. The proposed work will advance the collaboration between the Colleges of Engineering and Business at MSU.

Approach (Design and Methods)

Kramer, Xu, and Kesselheim (2012) conduct a systematic review of empirical studies evaluating medical device regulation in the US and the EU. They find that few studies have quantitatively assessed medical device regulation for either the US or EU systems, and these studies indicate suggest policy reforms are necessary for both systems. Three of the studies evaluated included surveys and interviews conducted by business consultants. These three non-peer-reviewed surveys indicate that the FDAs clinical data requirements, extended delay times, and inefficient processes are inferior to the EU system, weakened innovation, and harmed patients.

To the best of our knowledge, no studies evaluating the impact of biofilm regulatory policy on the development of healthcare-related products. In addition, no FDA-approved product has a biofilm claim associated with that approval. There are, however, 1914 new patents since 2001 that include the word 'biofilm' in the claim description, and 576 of these patents have been approved since January of 2014. Not all of these new patents are medically related, but many are. The numbers indicate a significant increase in the development of biofilm-related products.

The intent of this project will be to provide an initial attempt at better understanding the effects of regulation on the development of biofilm-related medical products. The methods used will rely on the approaches that have been developed to evaluate the effects of regulation on medical device development. This initial study will depend primarily on that work that uses surveys to examine the effects of regulation on medical device development. Some anti-biofilm technology has direct application to medical devices, for example, through application of medical device coatings to orthopedic medical devices or IV needles. Other applications, such as antibiotics, would be evaluated by the FDA as pharmaceutical products rather than medical devices.

The first step in the method will be to update the literature study of Kramer, Xu and Kesselheim (2012) to document the empirical and survey approaches that have been used to understand the effects of regulation on medical device development. This task will help us better understand the methods that successfully developed conclusions and recommendations regarding the effects of regulation on medical device development and will help us better develop a map for a successful analysis of biofilm-related projects.

To better understand the relative prevalence of the development of biofilm-related medical technology, we will evaluate the change over time of the number of US Patents that include the term 'biofilm' in the title, abstract or claims. This process will also include trying to identify which of these new patents are specifically for technologies that may have medical application that would be regulated by the FDA.

We also intend to attempt to map these medically-related to the FDA approval process. Unfortunately, this mapping likely will be very difficult because the requirements for an FDA application are very different from those of a patent application, and often the names of the technologies being developed are different between the two applications.

The majority of our efforts with this project will be to develop and administer a survey and questionnaire (to be administered verbally to those who would prefer it to an electronic survey) to evaluate the effects of regulation on biofilm-related medical products. This development of the survey and interview questions will rely primarily on the on the material from surveys developed by PriceWaterhouseCoopers (2011a, 2011b) and Makower et. al. (2010). Prior to administering, the survey and questionnaire will be vetted for content by biofilm experts from the CBE and by survey experts from the JJCBE.

We intend to administer the approved survey and questionnaire to a broad set of stakeholders in the development process for biofilm-related medical devices. These include government agencies (e.g., FDA, EPA), CBE corporate partners, state biotechnology development offices (e.g., Colorado Bioscience Association, Indiana BioCrossroads, Minnesota Life Science Alley, Montana Bioscience Alliance, Washington BIO), biofilm-related product developers (e.g., Bacterin, Microbion), and thought leaders in the medical biofilm industries.

Human Subjects – The proposed research does not involve human subjects.

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