Biofilm Control in Drug Manufacturing

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PREFACE

Microbial contamination of pharmaceutical products continues to be frequently cited as a reason for product recalls, manufacturing problems, and product rejection. Microbial contamination is costly to manage, time consuming to investigate and often difficult to determine root cause. The frequency of such problems, as well as the cost and investment of time and resources required to address them, support the need to develop and implement better microbial control programs that can more effectively prevent contamination from occurring.

As you will learn in various chapters in this book, biofilms are a preferred way of life for microbes and they are not only responsible for contamination in pharmaceutical and biopharmaceutical processing but also for many human pathogeneses including chronic wounds, device-associated infections, and various nosocomial infections and diseases in patients with compromised immune systems (Wilson, 2001). In fact, as reported in Infection Research (Kerksiek, 2008) estimates of the frequency of infections caused by biofilms (bacterial and/or fungal) lie between 65% (Centers for Disease Control and Prevention/CDC) and 80% (National Institute

of Health). In drug manufacturing, biofilms are known to impact equipment and systems, such as those used for water and product purification (e.g., filtration and chromatography). In addition, biofilms may lead to product adulteration, which can potentially cause patient harm. Therefore, understanding how microorganisms develop into biofilm cells, and the mechanisms of antimicrobial resistance present in biofilm communities, is critical for successfully controlling microbial contamination in drug manufacturing.

Over the years, many studies have been carried out in the areas of biofilm eradication, remediation, and prevention. However, the realization that biofilms are ubiquitous in nature and extremely difficult to destroy resulted in a shift in paradigm — from microbial eradication and remediation to biofilm prevention. Chapters 1, 4, 6, and 7 specifically address the importance of risk assessment and a proactive, rather than reactive, microbial control program.

On a molecular level, studies have been performed to better understand biofilm development. For example, in an article published in the *Journal of Bacteriology* (Branda et al., 2004), studies with *Bacillus subtilis* provided valuable information regarding the genetic control of biofilm formation, and showed that spore formation, long thought to be a process involving only single cells, is actually closely associated with the development of multicellular communities. There is particular interest on gene expression responsible for production of extra polymeric substances (EPS) and cell signaling/quorum sensing, both associated with biofilm establishment and growth (Hansen et al., 2007; Gonzales and Keshavan, 2006). Other studies include research with cyclic-di-GMP (c-di-GMP), which is a key player in the decision between motile planktonic and sessile microbial lifestyle. One study evaluated a chemosensory system that regulates biofilm formation through modulation of cyclic diguanylate levels (Hickman et al., 2005). Data suggested that increased c-di-GMP levels enhance biofilm formation, while decreased c-di-GMP levels prevent initiation of biofilm development. Researchers are also attempting to gain greater understanding of "persister" cells, which are specialized dormant cells proposed as the main reason for the refractory nature of biofilm infections (Keren et al., 2004). Chapters 2, 3, and 8 explain in further detail some of these ideas.

In terms of contamination control, the literature describes approaches to biofilm removal and prevention that range from the use of enzymes that can remove most, but not all, types of biofilms (Orgaz et al., 2007) to antimicrobial surfaces (Danese, 2002). Chapters 10 and 11 address sanitization approaches and studies in biofilm remediation and control.

Given the fact that the first step in biofilm formation is actually the ability to attach to a surface, and not microcolony formation or production of an EPS matrix, it is critical to investigate biological pathways used by bacteria to detect the presence of surfaces. Although the initial contact with a surface is not necessarily regulated and may happen by chance, there is evidence that formation of a stable cell-surface interaction may be genetically regulated (Stanley and Lazazzera, 2004). This is an important finding, because if surface attachment can be controlled, or even prevented, then all the other pathways to complete biofilm formation would be negated. Chapters 2, 5, and 9 help shed some light on these topics.

It is clear that biofilms are responsible for a number of serious contamination challenges in pharmaceutical/biopharmaceutical manufacturing, and the cause of several medical problems including chronic infections and medical device related infections. These complex and highly structured communities are difficult to prevent and even more difficult to eradicate. This book reviews the status of biofilm knowledge, management and control in pharmaceuticals, and is the first attempt to gather this type of information.

We close the book with an Appendix on resources that can be used by readers as a guide to general information about biofilms and related products.

A special note of gratitude goes to the authors who worked diligently to help make this book an excellent source of information for the pharmaceutical professional working in this area. Special thanks as well to our colleagues, associates, vendors and others who encouraged us and provided direct or indirect input to our work. We also would like to recognize Amy Davis — without her constant guidance and encouragement, this book would not be

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