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Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations

PDA Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations Technical Report Team

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1.0 Introduction

In the pharmaceutical industry, microbial-control issues are frequently cited in U.S. FDA inspectional observations and have resulted in recalls and/or medical shortages ***(1).*** In a review of more than 600 microbiology-related U.S. recalls of sterile and nonsterile products from 2004 to 2011, the majority resulted from a "lack of sterility assurance," indicating a potential problem with the product or packaging or that the manufacturer was unable to document that the product was manufactured in a state of control ***(2).*** Within the manufacturing environment, poor procedures, practices, and controls during the manufacture of sterile drug products and poorly designed environmental monitoring programs are frequent inspectional observations. Persistent bioburden and biofilm contamination have been implicated in at least one major recall that resulted in a medical shortage of parenteral products ***(1).***

Management of bioburden, primarily biofilms, in pharmaceutical production processes is a major focus of quality programs. Yet, despite the significant resources used in bioburden contamination control efforts, bioburden contamination of manufacturing processes can be a significant cause of compromised product quality and adverse regulatory findings. Reasons for the persistent challenge of bioburden control include production processes that support microbial growth, use of nonsterile source materials, and human interfaces. This challenge is further complicated by the ability of microorganisms to survive and often flourish even in harsh environments (e.g., exposure to chemical sanitizers and disinfectants, high shear, and pressure). The formation of complex, adherent bacterial colonies ("biofilms") in fluid handling systems is a common adaptive strategy for many microorganisms and presents a significant challenge for their detection and control. Microorganisms growing within biofilms, along with planktonic cells that are present in a bulk phase environment, comprise bioburden in fluid handling systems.

In the latter part of the 20th century, there was a fundamental shift in the understanding of microbial growth in various environments. The commonly held historical perception of bioburden was that it consisted of individual planktonic (free-floating) organisms. The planktonic model has been the basis for most current bioburden management strategies; nearly all of the commercially available bioburden detection systems are based on planktonic cell detection. However, evidence accumulated over the past three decades suggests that biofilms are actually the preferred mode of microbial growth ***(3-5),*** with sessile cells sometimes outnumbering planktonic organisms by several orders of magnitude in a given environment. Since the planktonic model does not provide for adequate detection and control of biofilms, there is a need for an increased focus on the development of effective strategies and techniques for the detection and control of biofilms in overall bioburden prevention and control activities.

Microbial and, in particular, biofilm control remains a major challenge for the medical device and pharmaceutical industries. Similarly, in hospitals and other healthcare institutions, a knowledge gap exists in the detection and control of biofilm-related infections ***(6).***

1.1 Scope and Purpose

A comprehensive program of bioburden management includes strategies for preventing and controlling biofilms and is based on current scientific knowledge of microbial growth and adaptation. This technical report presents the current scientific understanding of the causes of, and control strategies for, bioburden in pharmaceutical production systems, with a special emphasis on biofilms in fluid-handling systems. The scope of the report encompasses pharmaceutical and biopharmaceutical manufacturing processes but does not include final aseptic and terminal sterilization fill-finish operations. It is important to educate engineers, scientists and managers about the science of bioburden and biofilms because of the broad and complex challenge of bioburden management.