

Technical Report No. 51
Biological Indicators for
Gas and Vapor-Phase
Decontamination Processes:
Specification, Manufacture,
Control and Use



2010

Biological Indicators Task Force

Authors

Tim Coles, Pharminox Isolation (Cambridge) Ltd.

James Drinkwater, Bioquell (UK) Ltd.

Mike Edgington (Deceased)

Neil Grumbridge, Consultant (formerly with the UK Health Protection Agency)

Jon Nottingham, Cape Europe Ltd.

Emmanuelle Sansoë-Bourget, Altran AG Switzerland

Graham Steele, Ph.D., University of Bedfordshire

David Watling, Ph.D., Bioquell (UK) Ltd.

Contributors

Caroline Coles, B.A., Pharminox Isolation (Cambridge) Ltd.

Joseph Dalmasso, Ph.D., Apex Laboratories

Stewart Davenport, Pfizer

Kathryn Davies, B.Sc.

Didier Meyer, Getinge Life Sciences

Brian Midcalf, Ph.D., University of Leeds

Jeanne Moldenhauer, Excellent Pharma Consultants

David Morley

Murray Nicholson, Steris

Doug Thorogood, Ph.D., Eurostar

Ian Thrussell, MHRA

Peter White, Ph.D., Nova Pharmaceuticals

Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use

Technical Report No. 51

ISBN: 978-0-939459-32-2

© 2010 Parenteral Drug Association, Inc.

All rights reserved.



Table of Contents

<p>1.0 INTRODUCTION2</p> <p> 1.1 Purpose / Scope 3</p> <p>2.0 GLOSSARY OF TERMS4</p> <p>3.0 THE SCIENCE7</p> <p> 3.1 Sporicidal Mechanism of Lethality 7</p> <p> 3.2 Lethality Mechanism of Oxidizing Agents 7</p> <p> 3.3 Oxidation within Actively Metabolizing Cells.... 8</p> <p> 3.4 Lethality Mechanism of Alkylating Agents 8</p> <p> 3.5 Ideal Lethality Kinetics of Sporicidal Processes. 9</p> <p> 3.6 System D-Value Determination 10</p> <p>4.0 BIOLOGICAL INDICATOR DEVELOPMENT 12</p> <p> 4.1 Design of a Biological Indicator 12</p> <p> 4.1.1 Safety 12</p> <p> 4.1.2 Microorganism Selection 13</p> <p> 4.1.2.1 Desirable Characteristics of the Biological Indicator..... 13</p> <p> 4.1.3 Inoculum Pattern 14</p> <p> 4.2 Carrier Determination 14</p> <p> 4.2.1 Desirable Characteristics of the Carrier 14</p> <p> 4.3 Primary Pack Characteristics 16</p> <p> 4.4 Secondary Pack Characteristics 17</p> <p> 4.5 Compliance Objective..... 17</p> <p>5.0 MANUFACTURE OF BIOLOGICAL INDICATORS .18</p> <p> 5.1 Principles of BI Manufacturing 18</p> <p> 5.2 Starting Materials..... 19</p> <p> 5.3 Change Control 20</p> <p> 5.4 Production Process Stages for Spore Lots..... 20</p> <p> 5.5 Management of Master Seed Stock and Working Seed Lots 22</p>	<p> 5.6 Inoculation of Carriers and Assembly into the Primary Packaging..... 22</p> <p> 5.7 Factors requiring consideration When Using and Storing Bls 23</p> <p> 5.7.1 The Growth Media 24</p> <p> 5.7.2 Manufacturing In-Process Controls 24</p> <p> 5.7.3 Quality Control Methods 25</p> <p> 5.8 Storage and Distribution..... 25</p> <p>6.0 QUALITY MANAGEMENT26</p> <p> 6.1 Quality Assurance During Manufacture 26</p> <p> 6.2 Audit Documentation and Certification Requirements - User Audit of Supplier..... 26</p> <p>7.0 USE/APPLICATION28</p> <p> 7.1 Selecting the Appropriate Spore Type 28</p> <p> 7.2 Qualification of Bls 28</p> <p> 7.2.1 Enumeration and System D-Values 28</p> <p> 7.3 Cycle Development Studies 29</p> <p> 7.3.1 Cycle Development Approaches 30</p> <p> 7.4 Recovery of Bls 31</p> <p> 7.4.1 Sterilant Retained on the BI..... 31</p> <p> 7.5 Cycle Validation 31</p> <p>8.0 ADDRESSING ANOMALOUS BI RESULTS32</p> <p> 8.1 Investigation of Anomalous Results 32</p> <p>9.0 SUGGESTED READING.....34</p> <p>10.0 REFERENCES.....35</p>
--	--

FIGURES AND TABLES INDEX

<p>Figure 1.0-1 Biological Indicator Lifecycle2</p> <p>Figure 3.5-1 Idealized Plot of Death Kinetics....9</p> <p>Figure 3.5-2 Typical Survivor Curve 10</p> <p>Figure 4.2.1-1 Clean Spores on Stainless Steel Carrier 15</p> <p>Figure 4.2.1-2 Encrustation of the Spore Layer on Stainless Steel Carrier 15</p> <p>Figure 4.2.1-3 Clumped Spores on Paper Carrier 16</p> <p>Figure 5.4-1 Flow Chart of the Preparation of a Spore Suspension21</p>	<p>Table 7.1-1 Recommended Microorganisms.28</p> <p>Table 8.1-1 Factors That May Affect the Performance of Biological Indicators33</p> <p>Table 8.1-2 Manufacturing Issues That May Affect Bacterial Spore Resistance to Physical and Chemical Stresses33</p> <p>Table 9.0 Standards Relevant to Sporicidal Vapor-phase Decontamination Processes.....34</p>
--	--

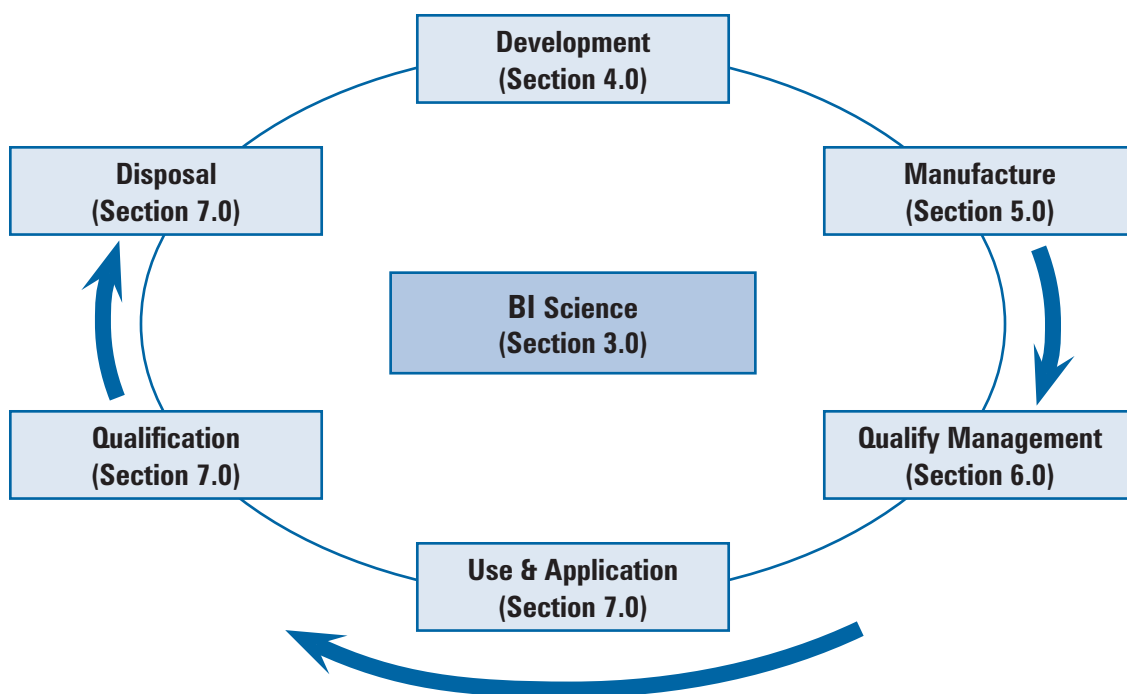
1.0 Introduction

Biological Indicators (BIs) are used during cycle development and the qualification of processes in which sterilization, sanitization, or decontamination is claimed. BIs currently are considered the only available tool capable of integrating the results of many parameters involved in achieving target kill at representative points throughout an enclosed space. These guidelines relate to sporicidal gas and vapor-phase decontamination processes where biological decontamination of surfaces inside contained volume areas is conducted. These areas include isolators, cleanrooms, containment rooms, and separative enclosures/devices. Some of these principles, however, may be applicable to the use of BIs for other processes.

This technical report provides a comprehensive review of an area not adequately addressed in current guidance documents. The report is intended to provide recommended specifications for BIs to be used with sporicidal gas and vapor-phase decontamination cycles together with guidance regarding their manufacture, quality control, and use. The principles described in this report are based upon the manufacture and use of BIs prepared from spore suspensions; however, they can be equally applied to the preparation of BIs from other sources.

Figure 1.0-1 illustrates processes regarding the science of BIs and specifications discussed in this report. Each subsequent process is then described, beginning with development and proceeding through manufacture, quality management, qualification, use, and disposal.

Figure 1.0-1 Biological Indicator Lifecycle



PDA requested the formation of a task force to develop a comprehensive set of guidelines to address the manufacture and use of BIs for sporicidal vapor-phase decontamination processes. The task force was composed of European BI manufacturers, academia, members of the pharmaceutical industry, and regulatory professionals. This report underwent a global technical peer review that included feedback from North America and Europe. References to regulatory documents, standards, and scientific publications are included to provide more detail and supportive data.