Technical Report No. 88
Microbial Data Deviation Investigations in the Pharmaceutical Industry
### Microbial Data Deviation Investigations in the Pharmaceutical Industry Team

#### Authors & Contributors

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julie Barlasov-Brown</td>
<td>Merck &amp; Co, Inc. (Co-chair)</td>
</tr>
<tr>
<td>Marc Glogovsky</td>
<td>ValSource, Inc. (Co-Chair)</td>
</tr>
<tr>
<td>Christopher Murdock</td>
<td>Ph.D., Bristol-Myers Squibb (Co-chair)</td>
</tr>
<tr>
<td>Ed Balkovic</td>
<td>Ph.D., Sanofi/Genzyme (retired)</td>
</tr>
<tr>
<td>Kim Sobien</td>
<td>PETNET Solutions, a Siemens Company</td>
</tr>
<tr>
<td>Thomas Arista</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>Tony Cundell</td>
<td>Ph.D., Microbiological Consulting, LLC</td>
</tr>
<tr>
<td>Osama Elrashidy</td>
<td>Bayer Healthcare (retired)</td>
</tr>
<tr>
<td>Dennis E. Guilfoyle</td>
<td>Ph.D., Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Jeanne Moldenhauer</td>
<td>Excellent Pharma Consulting</td>
</tr>
<tr>
<td>Jim Polarine</td>
<td>STERIS</td>
</tr>
<tr>
<td>Paula Peacos</td>
<td>ValSource, Inc.</td>
</tr>
<tr>
<td>Miriam Rozo</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Marsha Steed</td>
<td>National Resilience, Inc.</td>
</tr>
<tr>
<td>Jonathan Stewart</td>
<td>Cook Animal Health</td>
</tr>
<tr>
<td>Radhakrishna Tirumalai</td>
<td>U.S. Pharmacopeial Convention</td>
</tr>
<tr>
<td>Vanessa Vasadi-Figueroa</td>
<td>Quality Executive Partners, Inc.</td>
</tr>
</tbody>
</table>
Table of Contents

1.0 INTRODUCTION ................................................. 1
  1.1 Purpose ..................................................... 1
  1.2 Scope ....................................................... 1

2.0 GLOSSARY OF TERMS ........................................... 2
  2.1 Abbreviations/Acronyms .................................... 4

3.0 MICROBIOLOGIST ROLES AND RESPONSIBILITIES .......... 5
  3.1 Laboratory Microbiologist Responsibilities ............... 5
  3.2 Microbiologist Role in a Manufacturing Investigation .... 5
  3.3 Microbiology Laboratory Management Responsibilities .... 6
  3.4 Subject Matter Expert Responsibilities .................. 6
  3.5 Quality Control Unit Responsibilities .................... 6

4.0 PHASE I: CONDUCTING THE MICROBIOLOGY LABORATORY INVESTIGATION ................................................. 7
  4.1 Microbial Identification ....................................... 11
  4.2 Phase I: Specific Points to Consider ....................... 12
    4.2.1 Sterility Testing Investigations ...................... 12
    4.2.2 Bacterial Endotoxins Testing Investigations ........ 16
    4.2.3 Antimicrobial Effectiveness Testing Investigations ... 19
    4.2.4 Mycoplasma Testing Investigations ................... 19

  4.2.5 Biological Indicators Investigations ................. 21
  4.2.6 Aseptic Process Simulation Failures (Media Fills) .... 21
  4.2.7 Environmental Monitoring ................................ 22
  4.2.8 Utilities Monitoring ....................................... 23
  4.3 Phase I: Conclusion and Next Steps ....................... 24

5.0 PHASE II: MANUFACTURING INVESTIGATION .......... 25
  5.1 Root Cause Analysis ....................................... 26
  5.2 Phase II: Specific Points to Consider .................... 31
    5.2.1 Sterility-Positive Investigations .................... 31
    5.2.2 Determining Sources of Bacterial Endotoxin ........ 33
    5.2.3 Pharmaceutical Ingredient-Related Investigations .... 34
    5.2.4 Evaluation of Confirmed Mycoplasma Contamination .. 35
    5.2.5 Component (Container Closure) Investigations .......... 36
    5.2.6 Environmental Monitoring .............................. 37
    5.2.7 Investigation of Confirmed Contamination During A Process Simulation/Media Fill ... 39
    5.2.8 Utilities Monitoring ...................................... 40

6.0 CONCLUSIONS ................................................... 43

7.0 REFERENCES ..................................................... 44

FIGURES AND TABLES INDEX

Figure 4.0-1 Fishbone Diagram Showing Inputs of Microbial Testing during Root Cause Analysis .................. 7
Table 4.0-1 Sample Questions for Laboratory Investigations ................................................. 8
Table 4.1-1 General Points to Consider in Microbial Identification ............................................. 12
Table 4.2.1-1 Data of the Sterility Testing Facility Show a Fault ............................................ 14
Table 4.2.1-2 Testing Procedure Used Reveals a Fault ................................................. 15
Table 4.2.3.1-1 Questions Concerning Antimicrobial Effectiveness Testing ................................ 19
Table 4.3.4.1-1 Culture-Based Mycoplasma Testing Considerations .................................... 20
Table 4.3.4.1-2 Mycoplasma PCR-Based Detection Testing Considerations ................................ 21
Table 4.3.7-1 Environmental Monitoring: Questions Concerning Laboratory and Sampling ........... 22
Table 5.1-1 Factors to Consider in Root Cause Analysis ................................................. 27
Figure 5.1-1 Fishbone Diagram Examining Microbial Contamination of a Drug Product .......... 27
Table 5.1-2 Root Cause Evaluation and Follow-Up .................................................. 31
Table 5.1-3 CAPA Determination ................................................. 31
Table 5.2.1-1 Questions for Investigating Manufacturing/Process Sources Associated with a Confirmed Sterility Batch Failure ................................................. 32
Table 5.2.2-1 Endotoxin-Related Investigation Considerations .............................................. 34
Table 5.2.3-1 Additional considerations for raw material investigations ................................ 35
Table 5.2.6-1 Potential Sources of Contamination .............................................. 37
Table 5.2.6.2-1 Examples of Corrective Actions ................................................. 39
Table 5.2.7-1 Possible Origin of Representative Microorganisms .............................................. 40