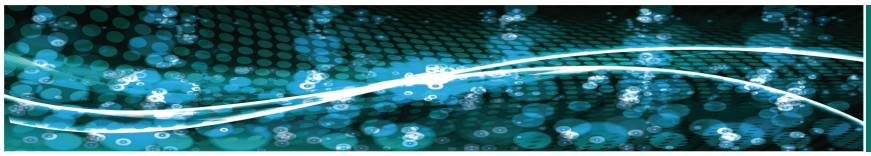

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WHITE PAPER

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A Strategy for Implementing Rapid Microbial Methods

Written by Gilberto Dalmaso, A & L Co. Industries
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About the author:

Gilberto Dalmaso is the manager of the Marketing and Sterility Assurance Consulting for A&L Co, a BioVigilant distributor located in Milan, Italy. Previously, Gilberto was part of the Aseptic QA and Biological Laboratories Group within the Quality Assurance Directorate for GSK Parma. While there, his main activity was to assure the microbiological quality of products within Parma facility and support Sterility Assurance. Gilberto joined the microbiological laboratory in Glaxo's Verona Italy site in 1984 where he implemented several improvements and innovations. In 2003, the Verona site was the first to obtain FDA approval for a rapid method now routinely used for WFI monitoring and the US release for a GSK nasal spray. In 2005, his team was the first to gain Italian regulatory approval for the parametric release for terminally sterilized products; and in 2008, obtained the first FDA approval for real-time release of a non-sterile product. In addition to his work with A&L Co, Gilberto is an ISO9000 Quality System inspector, a HACCP Inspector, and is active in the Parenteral Drug Association where he serves as member of the rapid microbiological technologies development and environmental monitoring group.

Rapid Microbiology

1. PURPOSE

The purpose of this paper is to present a strategy to be used and applied for rapid microbiological methods (RMM).

2. INTRODUCTION

There is a real and growing need in the pharmaceutical microbiology to introduce new analytical methods that can meet the requirements of the pharmaceutical industry. The current microbiological technologies are based on the 19th century. The continued use of these conventional methods proves how successful they have been in the pharmaceutical industry. Changes in the industry are beginning to happen. Technology-driven solutions to drug development and manufacture are beginning to take shape. The main regulatory agencies have recently published a series of guidelines with the purpose to facilitate innovation in the pharmaceutical industries.

If Good Manufacturing Practice (GMP) has been the light of Pharmaceutical Industry in the last 20 years, Quality by Design (QbD), i.e. how to build quality into the drug product, will be the new paradigm for the next years. This approach will have profound effects on the future direction of the industry. These changes will have an impact on every area of drug manufacture, including microbiological analysis. The new QbD processes will require real time or near real time analytical data and very different types of analytical evaluation. Current microbiological test systems will be unsuitable for many of the new applications as they are too slow and labour intensive and not capable of delivering real-time or near real-time results. It is no longer appropriate in a technology-driven industry of the 21st century to use 19th-century microbiological test methodologies. The stage is set for the implementation of a whole new generation of test systems in pharmaceutical analysis and this includes the evaluation of microbiological quality attributes.

New RMMs are emerging which offer the potential to provide

- rapid results
- real or near real-time data
- in-line or at-line testing
- automation and high test throughput potential
- high labour efficiency

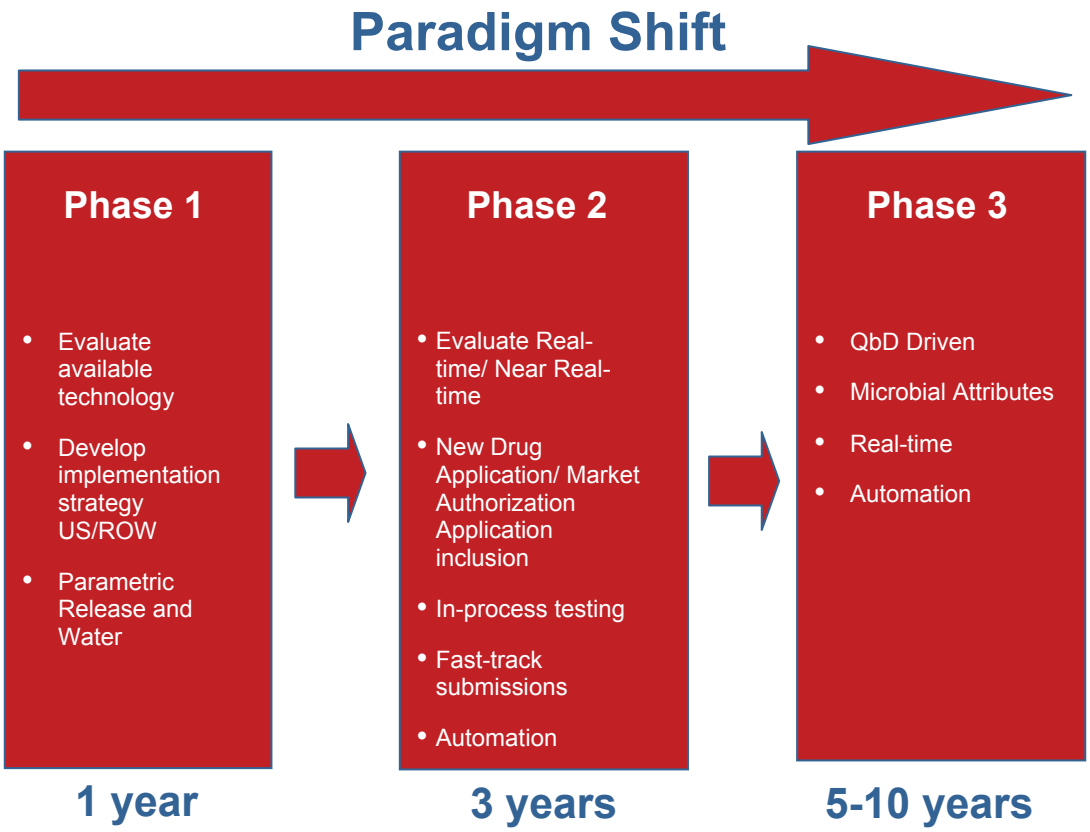
Interest in rapid microbiological methods in the pharmaceutical industry is high and is expected to increase following reports of successful implementation. Adoption of RMMs is warranted by significant advantages in speed of results, process efficiency savings, sensitivity, and business benefits.

The advent of QbD has given new impetus to the introduction of RMMs. Conventional microbiological test methods are not capable of delivering real-time or near-real-time results, a prerequisite for successful exploitation of QbD benefits. However, RMMs do have this potential and will be an invaluable aid to successful realization of QbD objectives.

The current situation for implementation of rapid microbiological methods is encouraging. New technologies for non-sterile product release testing and pharmaceutical-grade water testing have been approved in both the United States and Europe.

3. New Product Introduction RMM Strategic Model

The following scheme depicts the strategic model for the successful development of RMMs.



4. QUALITY BY DESIGN

Pharmaceutical Microbiology must examine its methods and ways of working if it is to respond to the pressures on tomorrow's industry. Even greater change will be required to satisfy the changes coming along in the not too distant future.

RMMs have a significant part to play in achieving QbD objectives.

Our quality system, in principle, is based on the foundation that "quality cannot be tested into products, it has to be built-in or has to be by design." However, significant gaps exist in the application of manufacturing science principles that suggests that this principle may not be optimally realized, i.e., the quality system tends to lean towards "testing to document quality." There are risks associated with this inclination that can be mitigated with an improved focus on manufacturing science to achieve QbD. A proposed definition for Process Analytical Technology (PAT) is **"Systems for analysis and control of manufacturing processes based on timely measurements,**

during processing, of critical quality parameters and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process."

The key words here are "*timely measurements during processing.''*

PAT requires that data generated during a manufacturing process must control the quality of that process. To move towards this vision a change is required which will provide process information for microbiological quality attributes which is beyond the scope of today's conventional methods. If QbD objectives and benefits are to be realised, the move to pharmaceutical RMMs is an essential requirement; QbD asks for faster, more accurate test methods capable of producing real-time or near-real time data for process control.

Until recently, PAT initiatives focused on chemical analytical techniques. However, what is the point of real-time analytical data if it only represents part of your process requirements. Microbiological data is an important quality indicator and an essential step in confirming process control. The FDA PAT subcommittee meeting held in October 2002 recognised the significance of RMMs and included them as a PAT tool for consideration. In September 2003, the FDA approval for the first PAT submission was for an RMM-based technology for non-sterile product release.

This has given new direction and meaning to the implementation of rapid microbiological test methods.

Furthermore, Janet Woodcock of the FDA, in May 2004, outlined the Agency's view for QbD:

- Stipulate (postulate) key performance parameters early in development process
- Design product & process to be robust for these parameters

5. CONCLUSIONS

Conventional methods of microbiological analysis in the pharmaceutical industry have been with us for many years and will continue for some time yet. They have been highly successful in determination of microbiological quality attributes for pharmaceutical processes and products. However, the pervading culture of the industry is changing. In the future, successful companies will need to re-examine their attitudes towards process efficiencies, risk-taking and technological innovation. These changes will undoubtedly affect the direction of microbiological analysis. Conventional methods will not be suitable for many future applications. The business drivers which have so far acted to maintain the status quo are changing:

- Industry attitudes and culture
- Equipment capital costs
- Managerial commitment
- Regulatory environments
- Unclear business benefits

Many of the issues above are being turned on their head. This is due to the emergence of new pharmaceutical manufacturing paradigms. The business environment has moved on and the need for solutions to cut costs and increase

competitiveness and efficiencies are irresistible. Pharmaceutical microbiology is part of this process. Obstacles still remain but implementation of RMM systems is beginning to happen. A unified European approach to fast-track new technology approvals would be a significant benefit to implementation of RMMs. The changes beginning to emerge across the industry represent significant opportunities which will undoubtedly aid the implementation of Rapid Microbiological Methods both now and in the future.

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