Encyclopedia of Rapid Microbiological Methods

Volume 4

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This volume is dedicated to the love of my life
and my childhood sweetheart, Christine,
whose inspiring support throughout the
years has provided me with the courage
and desire to follow my dreams,
both professionally and personally.

FOREWORD

Bryan S. Riley, Ph.D.

New Drug Microbiology Staff
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD, USA

Most of the history of microbiology as we know it has relied on the ability to visualize microorganisms following cultivation. Typically, cultivation has been done in a liquid medium such as a broth, or on a solid or semi-solid surface such as an agar plate (or in earlier times a potato slice). Although the ability to grow microorganisms is still an important aspect of microbiology, the time required for visible microbial growth (i.e., turbidity in liquid medium or a colony on solid medium) can be a hindrance in some circumstances.

The need for rapid results from microbiological tests has long been recognized by microbiologists in the clinical lab and the food industry. Rapid identification methods are now standard in the clinical microbiology lab. These methods range from automated variations on the traditional biochemical and phenotypic microbial identification tests to other rapid tests such as nucleic acid based methods (e.g., sequencing or microarrays) or Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI/TOF). Other rapid clinical tests utilize immunologic reagents to test for the presence of specific pathogenic microorganisms in patient samples. Some of these rapid tests are even used at the patient's bedside (or in the exam room), thus saving the time needed to transport the sample to the lab. The use of rapid microbiological methods has transformed clinical microbiology and improved patient care.

The food industry has also had a strong incentive for rapid microbial results. Screening tests for food borne pathogens must provide rapid results to ensure the safety of perishable fresh food. Waiting for potentially pathogenic microorganisms to grow on conventional media might not provide results quick enough to be truly useful. Rapid methods similar to those used in clinical microbiology are a mainstay in food microbiology and provide valuable information to protect consumers.

The pharmaceutical industry, in general, has not been as pro-active as the clinical and food sectors when it comes to rapid microbiological methods. The microbiological testing paradigm in the pharmaceutical industry has taken two pathways. The first of these has involved the microbiological release test (e.g., sterility or microbial limits). Although sterility tests take at least two weeks for final results, for most drug products it is not considered a problem to wait this long to release a batch of a sterile drug product. However, for some drug products, waiting several weeks for a traditional sterility test may not be practical. For example, for products with very short shelf lives (e.g., blood products, cell therapy products, and radiopharmaceuticals) two weeks might be most or even all of their useful life. Additionally, for some products manufactured in high volumes, the storage of product while waiting for sterility test results can be a significant expense and shortening that storage time could be economically advantageous to their manufacturer.

The other arm of the pharmaceutical microbiology testing approach involves in-process tests. This category of samples would include drug components, bulk drug product, environmental monitoring and water. All of these types of samples are currently tested for bioburden using traditional microbiological methods (typically plate counts) but the results are not available for at least several days. Meanwhile, manufacturing has moved on (perhaps all the way to a finished product) before the results of the microbiological tests are known. If the results of these tests are acceptable, this is a tolerable situation and the process is considered to be in a state of microbiological control. However, if any of these samples return results that exceed an alert or action level, then decisions must be made regarding the significance of these results and what affect they may have on product disposition. For a component like Water for Injection (WFI), a bioburden action level may affect multiple drug products produced using that WFI.

Modern approaches to process control (including Process Analytical Technology) require the availability of results in real-time (or at least close to real-time) to enable the operator to use the test results to make process decisions and adjustments. Although real-time results are only currently available for a limited category of microbiological tests, there are many microbiological

methods that are significantly more rapid than the traditional test methods. The rapid methods available today vary a great deal in their mechanisms of operation. Some of these methods still rely on a period of microbial growth using traditional media but reduce their time to result by using an alternate method of microbial detection. Other rapid methods do away with growth entirely and utilize a stain or inherent microbial auto fluorescence to detect microorganisms even down to the level of a single microbial cell. Some of the available methods are quantitative, some are qualitative, and they vary in their time to result (from real-time to several days) but all of these methods seem to have found a niche in the pharmaceutical microbiologist's arsenal. These current rapid microbiological test methods are now able to start providing some of the advantages (from a process control and economic return standpoint) long enjoyed by our colleagues in the clinical and food microbiology labs. Pharmaceutical microbiologists would be well served by considering which of their samples would provide a benefit with a more rapid result and then assessing the current alternate microbiological methods to see if any of them are a good fit for their needs. This *Encyclopedia of Rapid Microbiological Methods* will be an excellent resource to start that assessment.

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