Proposed Impact of USP Ch <1117>

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SUMMARY

As part of the regular review and updating of the *U.S. Pharmacopeia*, Chapter <1117> on Microbiological Best Laboratory Practices (USP 42 page 7713) was recently published for public feedback. In this article we will highlight major updates to the document and summarize some important areas of impact.

INTRODUCTION

To begin, what are good lab practices as defined by USP? This excerpt provides a good starting point:

Good practices in a microbiology laboratory consist of activities that depend on several principles: aseptic technique, control of media, control of test strains, operation and control of equipment, diligent recording and evaluation of data, and training of the laboratory staff. Because of the inherent risk of variability in microbiology data, reliability and reproducibility are dependent on the use of accepted methods and adherence to good laboratory practices. This is a major rewrite of the existing content of this chapter with new sections on considerations for risk assessment, method transfer, and data integrity.

Culture media are the basis for most microbiological tests so one likely impact on labs will be greater emphasis on uniformity of supply, as consistency in performance is critical. As Ch <1117> states:

Safeguarding the quality of the media is therefore critical to the success of the microbiology laboratory. Media preparation, proper storage, and quality control testing can ensure a consistent supply of high-quality media.

Clearly this poses not one but several rigorous challenges. However, a prime example of how they can be met is found in the growth media and cassettes of our Growth Direct® System. Produced in controlled cleanroom environments, each media-filled cassette is irradiated to ensure high quality and long shelf life while receiving a unique 2D identifier label; further sample identification can be provided with a system-generated, customer-applied barcode label. Once the cassettes are loaded, human handling is virtually eliminated with colony imaging, counting, and data recording all handled automatically. Sample integrity and staff safety can both benefit as a result.

USING MODERN TECHNOLOGIES

Going forward, proper training of your analysts and supervisors will be critical to the introduction and implementation of new technologies. As indicated below, Food and Drug Administration (FDA) auditors expect the staff working with new technologies to have a good understanding of the basics of the system and advanced features that differ from traditional test methods.

The use of new technologies in a microbiology laboratory requires new learning and training to ensure a proper implementation in the laboratory. In addition to the laboratory specialists, the laboratory

supervisors or quality assurance personnel evaluating qualification of systems or deviations must also have the skills to analyze and interpret the complex data that may be generated by new techniques. For each new technology, it is valuable to develop rules and principles that will build consistency and accuracy when laboratory personnel are using that technology to perform the relevant procedure.

Helping personnel adapt quickly to new technologies can be challenging, to the point that a given platform is only as good as the instruction that comes with it. Rather than risking false starts of incorrect implementation on your own, leveraging Rapid Micro's years of experience providing fast, efficient implementation support for many of the pharmaceutical industry's top companies can help you move forward with confidence.

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QUALITY REQUIRES BUDGET

The laboratory management is responsible for ensuring that the laboratory has sufficient resources to meet the existing testing requirements. This requires some proficiency in budget management and in determining appropriate measures of laboratory performance. A measure of laboratory performance is the number of investigations performed on tests conducted by the laboratory, but this measure alone is not sufficient. In addition to tracking investigations, the period of time between sample submission and initiation of testing should be tracked, as well as the period of time between end of test and report release (or test closure). Significant delays in these measures are also indications of an under-resourced laboratory staff. Particular measures of budgetary requirements will be specific to the given laboratory, ***but budgetary considerations related directly to the need of the laboratory for sufficient resources must be addressed to ensure reliable testing results*** [emphasis added].

METHOD TRANSFER

The most efficient way to recoup the investment in new technologies is to validate the first system then use a method transfer to roll the technology through the organization. The protocols for a method transfer are simplified versions of the initial-full installation and operational qualification (IOQ), performance qualification (PQ), and method qualification (MQ). The method transfer process can be completed in a much shorter timeframe, as proven repeatedly by Rapid Micro's validation team.

For analytical method transfers, comparative testing of the same sample may not be relevant for microbiological methods due to the non-homogeneity of microbial cells in the sample. Since no

contamination is frequently observed, such testing would result in comparing zero counts. Carrying out a method suitability verification of the analytical method of the product to be transferred would provide greater assurance that the transfer-receiving unit may adequately perform the tests under the conditions with the material used (e.g., nutrient media).

DATA INTEGRITY

With the introduction of automated-digitized raw data generation the controls move more to the software than just the analyst. This area has been the focus of much effort to define the requirements for data integrity, as it applies to microbiology. The recent PDA TR-80 technical report summarizes best practice in this area.

"The greatest data integrity threat with microbiological testing resides with falsification of data and intentional omission of testing results."

Microbiological methods are classically performed manually and on the basis of visual evaluation by an analyst performing the test. Therefore, the interpretation of test results or the number of colonies tested may be prone to a certain subjectivity and variability. To further improve data integrity and reduce subjectivity, alternative methods for the reading of plates, such as the use of automated plate readers or high-resolution photographs of the plate, may be used. However, these systems can have inherent challenges such as difficulty with the following: counting colonies embedded in the agar gel from pour-plated dishes, counting satellite colonies, differentiating overlapping colonies, differentiating particles from colonies, and interpreting the photo consistently from one individual to another. ***Automated enumeration methods that stack images to capture colonies growing in time may overcome some of these challenges*** [emphasis added].

Counts from Petri plates are considered original data on the day that the method requires the plates to be read and recorded. After reading, if these same plates are subsequently stored at room temperature or under refrigeration, it is not possible to confirm the original results because the microbial counts may increase during storage.

It is common practice for the raw data sheet that contains the original data, as well as the data entry from the raw data sheet to the laboratory information management systems (LIMS), to be reviewed for accuracy and completion by a qualified analyst, an analyst who has not executed or evaluated the test, or the supervisor.

The greatest data integrity threat with microbiological testing resides with falsification of data and intentional omission of testing results. To control this risk, the company culture and ethical standards are essential as well as the application of a rigorous quality management system.

RISKS WITH MANUAL PLATE COUNT

Ch <1117> concedes that using a "four eyes" approach gives better control in theory; however, the practical implementation can negate the benefits. Analyst variability and the timing of each read can create aberrant data. The use of automation and fully validated vision algorithms remove any doubt to the result through the forensic audit trail, from the time the sample is loaded in the Growth Direct® System through to the complete test cycle when a secure result is logged into the central database software manager.

For the compendial sterility test that combines criticality of the test and higher risk of misinterpretation of results, it is now a standard practice to have a second analyst perform a contemporaneous evaluation of the sample (in test media) for microbial growth. Nonetheless, applying uncritically a contemporaneous

reading by a second analyst (four-eyes principle) for all samples and microbiological tests is not recommended. Precision in counts may vary from one analyst to another (even if they are trained and qualified) as colonies may overlap, swarm over media, etc., allowing for misinterpretation. Microbiology is a "logarithmic science"; sample size is statistically weak and testing procedures have inherent variability. By tolerating no differences in counts, a high number of non-critical deviations will be generated, thus consuming resources unreasonably. As an alternative to a contemporaneous enumeration, a contemporaneous verification by a second person that the testing activity is performed correctly may be executed for higher risk tests. A second person could verify, for instance, if the reading of results is correctly executed according to the procedure, if the result on the Petri plate is correctly transcribed onto the GMP recording sheet.

HOW TO TAKE THE NEXT STEP FORWARD

If you and your team find it challenging to define and adopt today's best practices, contact Rapid Micro Biosystems today. Our experienced support professionals can help you make sense of regulatory complexities, exploring the Growth Direct® System as you strive to make your lab more efficient and effective.