Process Analytical Technology Initiative
Rapid Microbiology Methods

Rapid microbiology methods have been a goal of manufacturers because of the time required to perform conventional testing, which is dependent on microbial growth to make the microscopic become visible. New methods can reduce the time to obtain results from several days to a few hours. Under these circumstances, new methods may allow manufacturers to detect adverse trends early and make corrections before they endanger products or processes. By analogy, rapid methods in clinical microbiology identify microorganisms and allow physicians to begin treatment more quickly.

Implementation of new microbiological methods poses significant problems and risks. These include validation of methods that will not yield results equal to traditional methods. Additionally, comparative parallel testing is not always informative. Experimental designs for validating the methods can be developed, but may not be a perfect solution. Therefore, some risk is involved and there is a need to create a "safe harbor" for firms willing to undertake new microbiological tests.

The safe harbor concept for sterility testing using new/rapid microbiological test methods (a specification change using the ICH definition of specification) may be limited because the test is qualitative and the established release test requirement is a critical parameter. For a critical parameter, the batch cannot be released if the parameter is not met. The safe harbor concept for sterility testing may not afford much latitude because a failed criterion prohibits retesting by the same method or even a compendial method. The batch must be rejected. Otherwise, the batch is "tested into compliance."

Quantitative (such as microbial limits tests for total counts or total fungi, or environmental monitoring) may be suitable for the safe harbor concept. Parallel testing and retesting might be considered since the counts and acceptance criteria may be based on different units of measure. Quantitative limits may be developed from parallel testing to establish reliability of a new test method and correlation of the acceptance criteria. Experimental methods involving challenge and recovery studies may also be developed to validate new microbiological test procedures.

New/rapid microbiology methods seem least controversial for in-process tests. These tests measure the state of control of a process rather than a finished product. New baselines for process indicators may be established without a problem, but an awareness of the difference is needed by regulators and manufacturers. Manufacturers initiating such testing should expect the minimum delay when implementing these tests with adjusted acceptance criteria. Discussion of whether the safe harbor initiative should allow retests as part of an investigation of an in-process test result should be undertaken.

Discussion Topics for the Breakout Session

1. Can validation of new methods employ laboratory models to demonstrate assay suitability? How can new acceptance criteria be established using different measures?

2. Should there be application of the "safe harbor" concept for sterility testing (something other than batch re-testing)?

3. If a failure situation develops in quantitative product tests (e.g., microbial limits), should the "safe harbor" concept include retesting by either the compendial method or by repeating the new/rapid method?

4. Should firms be permitted to return to traditional methods (without prior FDA approval) if the new method proves unsatisfactory?

5. To encourage implementation of rapid microbiological methods as part of the PAT initiative should FDA embark on specialized training of field and review staff, or establish a specialized team to address these techniques? How could this be accomplished?

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