Rapid Microbial Testing: Overcoming the Barriers to Adoption

By David Jones at Rapid Micro Biosystems

Rapid microbial testing methods can deliver tangible benefits throughout the pharmaceutical manufacturing process – but if manufacturers are to adopt such methods in preference to traditional culture testing, then various barriers need to be overcome.

The manufacture of pharmaceuticals is a complex and highly regulated process. The faster that a profitable new drug is brought to market, the greater the revenues – but the process can be slowed by a variety of hurdles. One area of delay for pharmaceutical manufacturers is the quality control (QC) steps that must be performed throughout the manufacturing process, as these can significantly prolong the manufacturing release cycle.

The visual culture method used today for bioburden, environmental monitoring and sterility testing takes days to weeks to obtain results. For example, vaccine producers must wait 14 days for sterility test results during the manufacturing process, and then again before release of the final vaccine to the public. The use of rapid methods during these steps can reduce time and error; however, most companies still use methods that were popular in the 19th century.

It is generally known that pharmaceutical manufacturing is divided into phases such as the raw materials testing phase, the in-process phase, the packaging phase and the final product release phase. During these stages, quality control testing is required to ensure product safety and so, for each of these areas, the benefit of a rapid method is clear.

In-Process Phase: Raw Materials Testing

During the in-process phase, it is common to test the combined raw materials to ensure that product is within acceptable constraints. For liquid products, this generally involves bioburden testing that involves filtering the sample through a membrane and then incubating the sample for a certain time period (typically 5-7 days). During this time, the manufacturer can either wait to continue production, or carry on producing product at the risk of potentially having to discard the batch if contamination occurs. This can become costly with high-value products, or could cause unnecessary delays in manufacturing.

Changing from the culture method to a rapid method could streamline this process. Even a final result in half the time (2.5-3.5 days) can have a significant impact on manufacturing times. If the rapid method included an element of automation, then this could also free resources in the quality control area for higher-value activities.

In-Process Phase: Environmental Testing

Throughout the manufacturing process, regulations require that the manufacturing environment be regularly monitored for potential contaminants. These tests include the monitoring of surfaces in the manufacturing area, the air inside the manufacturing room and the personnel working the manufacturing area. Samples are often captured via a contact plate and incubated for around five days. Similar to the materials testing, contamination in the environment can grind production to a halt.

Using the existing culture method as a basis for sample capture, in combination with automated rapid technology for analysis could accelerate results, providing positive results within hours and final results in half the traditional incubation time. Again, the impact on manufacturing is significant. With results available in hours, the organisation can quickly respond to a contamination event. Automation also provides value as the environmental monitoring tends to involve a large number of sample data points that must be analysed and plotted as part of trend analysis.

Release Testing

With certain types of pharmaceutical product, a sterility test must be performed before releasing the product. This test traditionally takes 14 days, and failure of a sample can have a significant impact on the organisation. Rapid detection methods that match the

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complexity of the current test (aerobic and anaerobic at two temperatures) and give a positive result within hours and final results in half the traditional time, can help manufacturers determine sterility failures more rapidly – shortening the time to market for a product.

Why Manufacturers Use the Culture Testing Method

In quantitative applications, the regulations specify traditional colony counting as the reference microbial enumeration method. For qualitative or presence/absence testing, the regulatory compendia call for culturing microbes in liquid broth culture. These culture methods detect microbes by allowing them to grow in the presence of nutrient medium until they can be visualised by eye.

The dominance of the culture method in pharmaceutical quality control testing for more than 100 years stems from its many substantial advantages; these include its sensitivity, low cost, ease of use and status as the regulatory reference method. However, traditional growth-based tests are slow, requiring several days to weeks to return results, and it is this slow test turn-around that leads to a delayed release of safe products. Rapid testing technologies are available to manufacturers but their adoption has been limited. One factor impeding adoption of these new methods is the need to demonstrate that the results obtained using the new system are equivalent to those using the compendial culture method. Some of these technologies do not uniformly deliver equivalent results (delivering a different quantitative result), many lack the sensitivity of the culture method, and many do not uniformly detect all types of microbes or are incapable of detecting microbes in all types of sample. Finally, many current rapid microbial testing methods destroy the microbe, or require recovery techniques that may not be considered robust and reproducible. When a test is positive, manufacturers are expected to identify the organism present in the sample as the first step in their root cause analysis in order to establish appropriate corrective action. To ensure the microbe is available to identify, manufacturers have stayed with the proven culture testing method.

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Addressing the Obstacles to Adoption

At Rapid Micro Biosystems, our research with customers, focus groups, online surveys and industry research, such as those provided by Strategic Consulting, Inc (1), identified key issues hampering the adoption of rapid methods. A rapid technology that contained the following features could overcome the existing obstacles and replace the traditional culture method:

- Ensuring that sample preparation mirrors the current method. Given the complexities in sample preparation in sterility testing, and the high volumes of samples in environmental monitoring, the preference is to use methods that closely replicate existing sample preparation. This simplifies training.
- Minimising the system footprint and maximising the efficiency of the automation.
- Providing flexible and easy-to-use technology so that a user can load the technology and then walk away. While a rapid answer is important, the quality control lab operates with a limited set of resources. Any automation that frees up resources would be valuable.
- Supporting the unique needs of sterility testing (closed loop testing) and environmental monitoring (air, surface, personnel).
- Providing sample for identification. In the event of a variance, the quality control lab must perform an investigation, which may include an identification of the contaminant. Having a sample available for identification solves this problem.
- Incorporating 'lean lab' initiatives. The last few years have seen an increase in the need to drive efficiencies in the QC lab through initiatives such as 'lean lab'. A method that includes automation to eliminate wasteful steps and improve efficiency would be a positive factor in adoption.

Conclusion

Rapid microbial testing methods can deliver tangible benefits throughout the pharmaceutical manufacturing process; however, many businesses continue to use the time-consuming, traditional culture testing method. Several roadblocks exist to the further adoption of rapid methods – but a technology that addressed these barriers would drive higher levels of adoption.

Reference

1. Strategic Consulting, INC 2010, Pharma/PCP – 2nd Edition, *Global Review of Microbiology Testing in the Pharmaceutical and Personal Care Products Industries*, Strategic Consulting, INC 2010; 5.8-5.10