Bioprocessing

The Lean Microbiology QC Lab

By David Jones and Mark Severns at Rapid Micro Biosystems

Microbial quality control has been left behind with the same methods being used as over 100 years ago. However, the arrival of automation is propelling the Micro QC lab into the 21st century, driving significant improvements in efficiency and productivity.

Automation changes the way we think about processes. Since systems function more smoothly when they are fed with a continuous supply of work, every aspect of the system can be kept running at 100 per cent capacity over 24 hours. Automated systems deliver maximum process savings and return on investment (ROI) when the supporting manual processes are also optimised to support the automation, thus minimising the need for an analyst's time and effort.

The last 100 years have seen exponential growth in technology and automation. At the start of this period, Henry Ford developed his version of the assembly line, revolutionising methods of mass production. At that time, the word 'automation' meant conveyor belts, not computers or the modern automation we know today. For the pharmaceutical industry in particular, the quality and availability of products have increased radically over the last 100 years, and the pharmaceutical manufacturing facility is now a testament to modern automation. But business must continue to innovate to ensure progress.

The pharmaceutical industry is under extreme pressure to get products to market faster to maximise the value of drugs on patent. The traditional model for pharmaceutical companies has been to spend significant amounts of time and money on developing a drug, and then, while the clock counts down on their intellectual property, the business drives billions of dollars annually from the protected revenue stream. When the patent expires, there is still a gentle trail off of revenue. This environment has changed, however. Today, there is tremendous pressure on the traditional model from all sides, including pricing, competing medicines, payouts and generics. Over the last decade, concepts such as lean manufacturing and six-sigma have driven efficiencies in manufacturing. Quality control (QC) laboratory activities, however, have generally gone un-recognised as a contributor to these efficiency challenges, but that perspective is changing.

MICROBIAL QUALITY CONTROL

One area of pharmaceutical manufacturing that seems to be stuck in the past is microbial quality control (Micro QC). For over 100 years, the traditional culture method has been the accepted technique for routine pharmaceutical and biological quality control testing. The test is inexpensive, but requires time for the contaminating organism to grow to a level capable of being detected by the human eye. During this time, product could be waiting in quarantine, or production could be stopped, waiting for a component to pass inspection. This practice creates the perception that Micro QC is a bottleneck to the otherwise streamlined manufacturing process.

In the Micro QC lab, the microbiologist struggles to complete low value, tedious tasks. Consider a seven-day water or bioburden test, a common test for liquid pharma manufacturers:

- On day one, the microbiologist has to pull together paperwork for the test, fill out the assay info, prepare the sample, and load the samples into the incubator.
- Often to aid production, samples are pulled on day three for an interim result. This means the microbiologist has to pull the samples, perform the counts, record those counts and return the samples. By day three, there is usually a need to shift samples around in the incubator, which takes time – more samples have been taken in the interim that fill the incubator.
- Finally on day seven, the samples are pulled and counts are performed and recorded, with the final counts likely to be keyed into a LIMS system. The sample plates are then either disposed of or taken to be identified.

While this may not seem like a lot of work, consider that this can happen with between 8,000 and 12,000 samples during the course of a year, and that this is only part of the microbiologist’s role. Manual processes create possibilities for human error, requiring time-consuming investigations. Key examples of errors seen in the Micro QC lab are incubation of plates at the wrong temperature or for the wrong length of time, recording data to the wrong sample ID, and mistakes...
in transcribing counts to the batch record or LIMS. The Micro QC lab is therefore a prime candidate for automation.

**THE LEAN LAB**

Fortunately, new initiatives have started to reach the Micro QC lab. The concept of the ‘lean laboratory’ has started to take hold and drive new efficiencies in the QC lab. This concept focuses on the use of less effort, fewer resources and less time to test samples. One area of focus is the elimination of waste and wasteful practices.

Considering all the wasteful steps in the previous example, there is significant opportunity for the Micro QC labs to take advantage of lean labs.

To support these initiatives, new technologies for the rapid detection of microbial contamination in the pharmaceutical Micro QC lab are playing a strategic role in improving the time to results of an inspection, allowing product to pass quality control earlier than was previously the case. While rapid detection alone can solve part of the problem, it still leaves the QC lab with a labour-intensive process that, because of the human element, is still prone to errors. The manual process causes highly trained microbiologists to become bogged down with running tests rather than focusing their data analysis and problem solving skills on more value added activities to drive business productivity.

Automation of the Micro QC lab takes rapid detection to the next level, allowing the lab to benefit from automation – much like their counterparts in the analytical chemistry QC labs and in manufacturing. Automated rapid detection removes cumbersome steps in the testing process, as well as driving efficiency and productivity. The process offers benefits in a number of areas:

- Faster product testing – as a result of products coming out of quality control more quickly, the business can realise a reduction in inventory in the first year
- Contamination – in raw materials, in-process batches or finished drug products can be detected more quickly. Because contamination is uncovered faster, less product is contaminated resulting in less scrap
- Plant start-ups – rapid detection reduces the number of days required to restart a plant after a shutdown or line change. This allows faster return to service and results in increased manufacturing days
- Process automation – because the microbial test process is automated, the time spent on sample manipulation, LIMS data input, as well as reporting and auditing of test results is significantly reduced

To quantify the gains in efficiency, the estimated annual savings a biologics manufacturing plant producing an injectable pharmaceutical product would be $2.9 million. These savings come from a combination of areas, including:

- Faster detection of raw material contamination
- More rapid facility changeovers
- Rapid detection of in-process failures
- Labour savings from the automation of steps

These numbers create a compelling reason to research automated rapid microbial detection for the Micro QC lab.

**CONCLUSION**

One area that has been overlooked for process improvements and better ROI is the microbial quality control process, which still operates using principles from over a century ago for sample analysis – a labour-intensive and error-prone process that creates an unnecessary risk for the pharmaceutical manufacturer.

What HPLC brought to the analytical lab, automated microbiological methods can bring to the Micro QC lab. HPLC replaced manual wet chemistry and multiple process steps, resulting in an improved quality of data management with lower error rates and greater reproducibility. Automated rapid micro methods provide real, quantifiable results for the manufacturing process – making it an exciting time for the Micro QC lab.

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