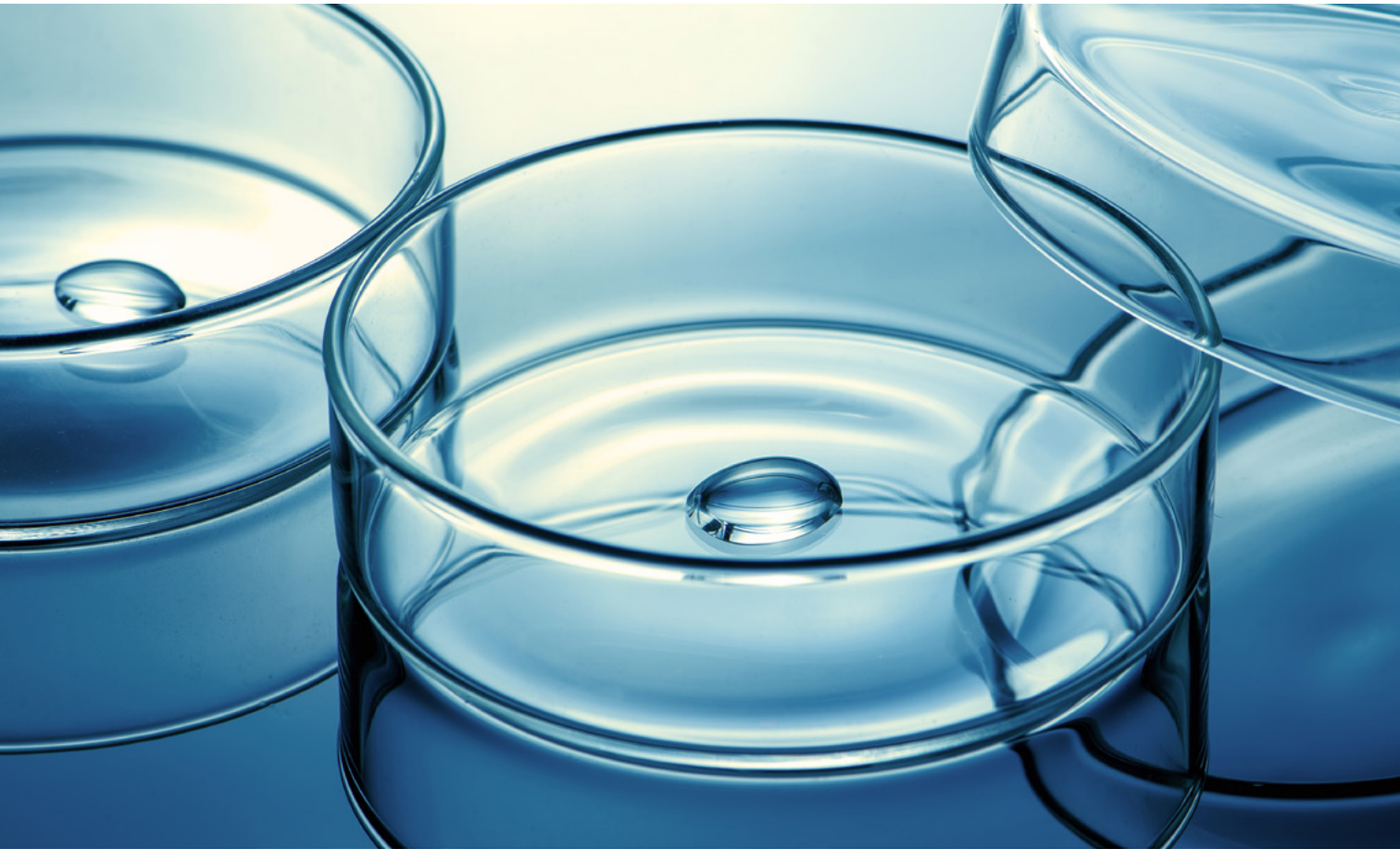
pharma MANUFACTURING
SPECIAL REPORT

The true value of real-time **microbial monitoring**



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The true value of real-time microbial monitoring

Recent study reveals the hidden costs of manually managing pharma waters

In the U.S., the use of bacterial plate counting methods for water system analysis goes all the way back to a reference guide first published in 1905.*

Now, 23 editions and 117 years later, manufacturers are still using similar methods to monitor the microbial health of pharma water systems, despite known inefficiencies.

This traditional monitoring method involves taking a grab sample from a point of use on a timely basis, and incubating for at least five days to determine microbial excursions. But with many pharma manufacturers operating sophisticated (and costly) continuous water purification systems, results that come days after a sample's been taken do little to ensure confidence that water being used — or even water that has already been used — in production is safe and on spec.

Fortunately, instrumentation that enables at-line or on-line microbial monitoring is available to fill the gaps left by traditional methods. To understand the true value of adopting real-time microbial monitoring, Pharma Manufacturing and Mettler Toledo conducted an industry survey of water system and process control professionals looking at how companies monitor for contamination, and the impact of their methods on microbial investigations, additional sanitization efforts and false-positive contamination results.

Ultimately, using real-time monitoring leads to less costly problems — and less problems overall.

The survey found that, while the cost of real-time monitoring technology is a major barrier to adoption, users who continue to only use the plate count method in their microbial monitoring process generally have more contamination investigations, higher false-positive rates and greater costs associated with extra sanitizations. Ultimately, the survey revealed that using real-time monitoring leads to less costly problems — and less problems overall.

CURRENT STATE OF MICROBIAL MONITORING IN PHARMA

When it comes to pharmaceutical waters, the stakes are high. For drugmakers, it is not just about meeting stringent pharmacopeial requirements — the quality and safety of finished drugs, and thus overall patient health, rely on the purity of water used in production.

In contrast to the batch system used to make most drugs, water production in the pharma plant is continuous, with water re-circulating and consumed regularly. This means that water purity needs to

* Standard Methods for the Examination of Water and Wastewater was first published in 1905. Since that time, and through 23 editions, Standard Methods has included hundreds of analytical techniques for the determination of water quality.

be monitored constantly. Traditionally, samples are taken from the line and sent to a laboratory for testing. Our survey found that 43% of plants still rely solely on this method — using only grab samples for microbial testing of high purity waters, such as Purified Water or Water for Injection. (Exhibit 1)

Once the samples arrive at the lab, almost 70% of plants still employ some degree of manual plate counting to measure microorganisms present. The possibility of human error is high with manual colony counting and this could trigger data integrity issues with the U.S. Food and Drug Administration (FDA). In fact, it is not uncommon to see issues with plate counting featured in FDA warning letters.

To combat this issue, our survey found that 23% of plants have automated the process, turning to automated plate counters. While this technology eliminates some of the human error potential seen in manual plate counts, it is still not without its challenges in terms of validation, especially when used in a GMP environment.

The good news is that some pharma companies are taking the automation a step further by using rapid microbial methods for water monitoring. Over 43% report using a combination of grab samples and on-line/at-line monitoring of manufacturing processes. (Exhibit 1)

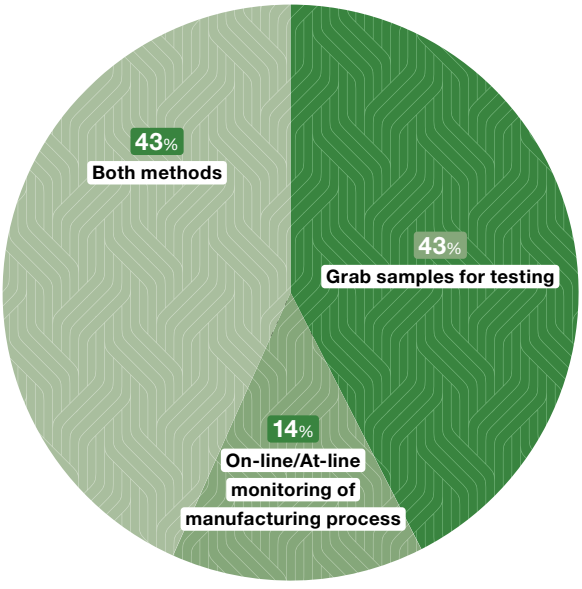

EXHIBIT 1

What method are you using for microbial sampling of your Purified Water or Water for Injection?

~25% of plants face more than five investigations per year for positive microbial tests.

LINK BETWEEN MANUAL METHODS AND INVESTIGATIONS

Despite some encouraging steps being taken towards automating water quality management, pharma manufacturers are still dealing with potential microbial contamination events. Our survey indicated that roughly 25% of plants face more than five investigations per year for positive microbial tests. (Exhibit 2)

When asked to provide an example of the type of situation that was determined to be the cause of microbial excursions in their plants, several respondents mentioned biofilm. “A biofilm developed over time with excursion above alert/action limits, requiring sanitization of the water system and testing of finished product,” said one respondent.

Because biofilm — which can appear on the surfaces of things

like pipes or valves or at the point of use — grows gradually, it is often not captured by more traditional plate counting methods. On-line or at-line testing increases the possibility of detecting biofilms early.

Interestingly, of the facilities reporting the most yearly investigations for positive microbial tests (16+ investigations), none said they were using on-line/at-line monitoring of process parameters to ensure their water quality. Instead, the plants reporting these large numbers of excursions said they were testing final or intermediate products or water samples in a lab.

These results are encouraging, in that they imply that real-time monitoring of process parameters can lead to less microbial investigations for pharma manufacturers.

THE HIDDEN COSTS OF INVESTIGATIONS

When a microbial excursion is discovered during water testing, how do pharma plants proceed?

While pharma facilities typically have detailed, multi-step standard operating procedures for microbial investigations, 70% of those surveyed said these procedures involve extra sanitization. (Exhibit 3) Sanitization is already a major expense for pharma companies — consuming water, electrical energy and time — and it follows that added sanitization adds to those expenses.

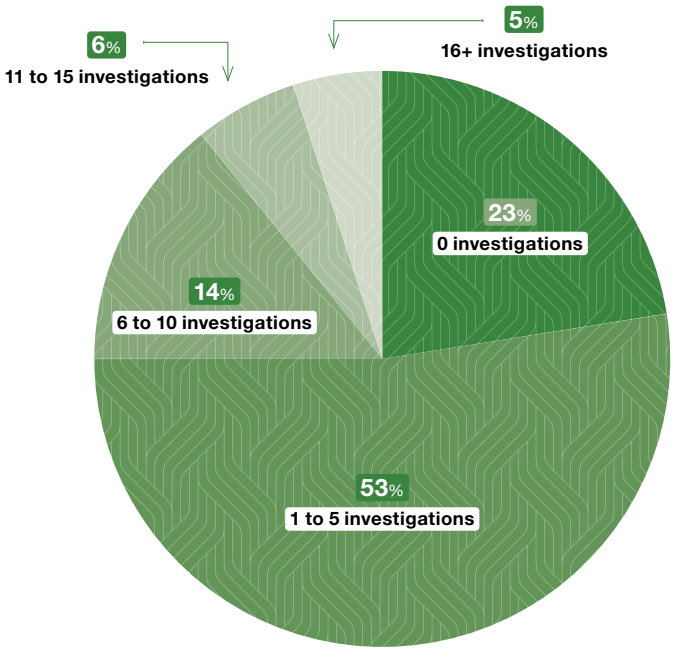

EXHIBIT 2

On average, how many investigations for a positive microbial test occur per year at your facility?

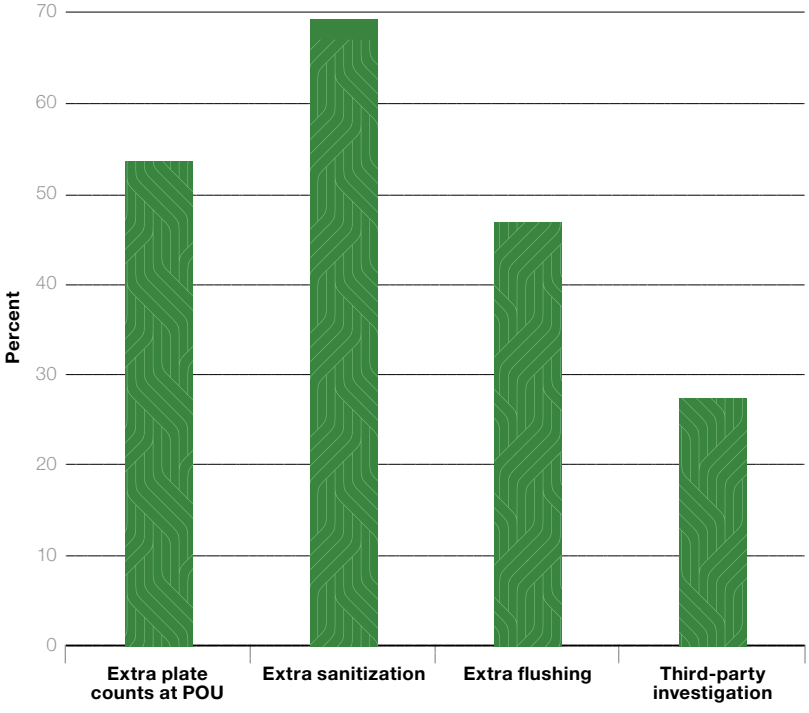

EXHIBIT 3

What steps do you follow when you have a positive result (a microbial excursion)? (check all that apply)

Timely and effective investigations of any microbial event are crucial so that corrective actions can be taken swiftly. Our survey found that more than half of plants perform extra manual plate counts at points of use in response to a microbial event — a time- and resource-heavy process. Microbial excursions could necessitate stopping the production line so that the water system can be thoroughly inspected, a process that may require days of lost production if manual monitoring methods are used.

Ultimately, if plants are not continuously monitoring the health of water systems in real time, any microbial excursion means multiple decisions need to be made regarding the water and the product that came in contact with the water since it was last tested — and all of these decisions come at a cost.

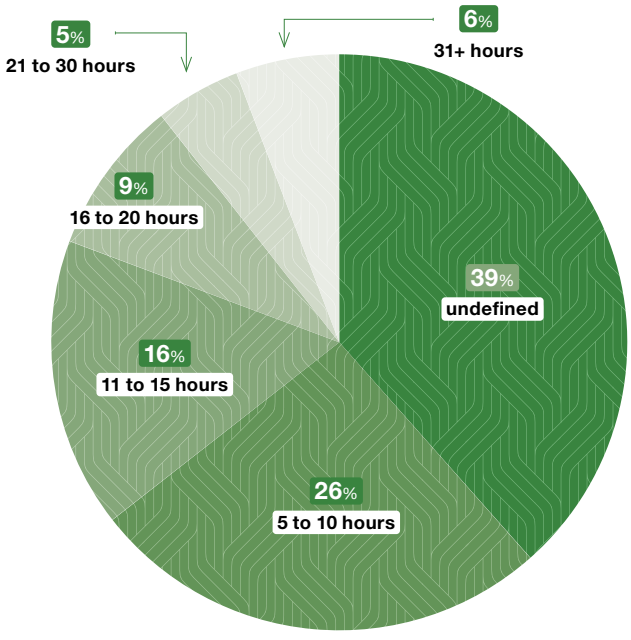

EXHIBIT 4

How many production hours are lost due to a false positive investigation?

THE PRICE FOR FALSE ALARMS

It is not uncommon for "positive" results from point-of-use microbial tests to end up being false-positives. This can be caused by sampling errors or sample contamination from the technician, sample container or environment.

About a quarter of the plants surveyed found that, upon investigation, more than 10% of positive microbial tests were subsequently determined to be false-positives. And over 10% of respondents said

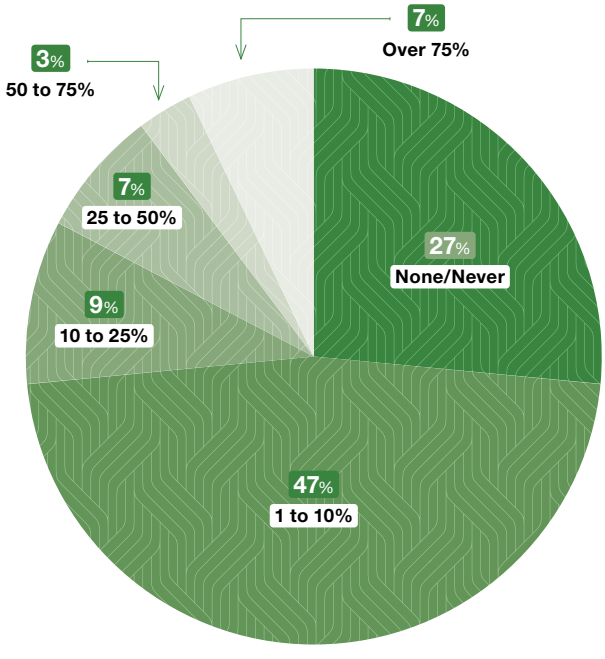

EXHIBIT 5

What percentage of positive microbial test are subsequently determined to be a false positive?

that a whopping 50-75% of positive microbial tests are later found to be false-positives. (Exhibit 5)

These investigations can be costly in terms of production hours. Over one third of those surveyed said they lose more than 10 hours of production time investigating false-positives. And just over 10% of those surveyed report a loss of more than 20 hours of production time due to these investigations. (Exhibit 4)

In addition to lost production time, survey respondents indicated that microbial investigations — whether they are later determined to be false-positives or even false-negatives — don't come cheap in pharma. According to survey data, a single investigation can cost a drugmaker as much as $50,000. This estimate includes the cost of retesting, as well employee time needed to conduct the investigation and prepare associated reports.

Over 42% of water quality professionals estimated costs per investigation in the range of $5k to $20k. Over 15% put costs anywhere from $20k to as much as $50k. (Exhibit 6) Real-time monitoring, however, appears to lower the costs of investigations. Over 75% of those who monitor water quality process parameters in real time report that investigations cost under $10k.

All things considered, the total cost of microbial excursions — even if they are subsequently determined to be "false alarms" — is significant.

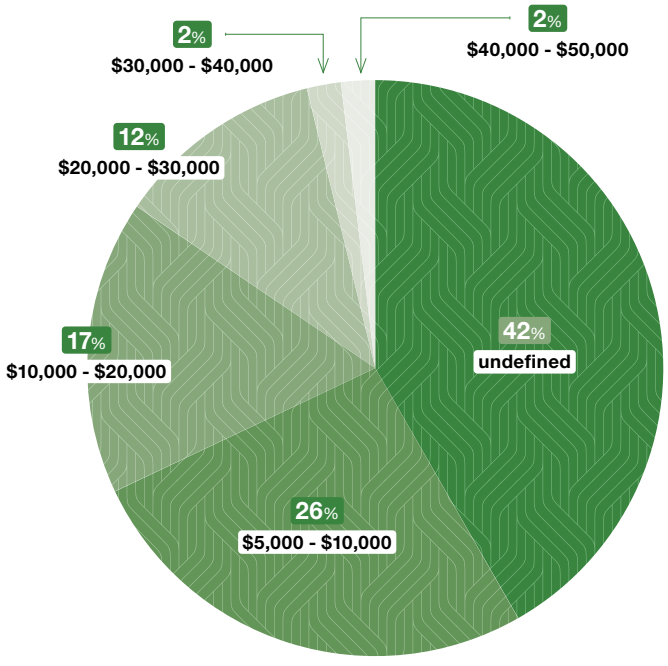

EXHIBIT 6

What is the cost of a false positive/false negative investigation each time? Consider the cost of retesting and the number of persons involved in the investigation and report preparation.

Over 75% of those who monitor water quality process parameters in real time report that investigations cost under $10k.

WHAT'S HOLDING PHARMA BACK FROM ADOPTING NEW METHODS?

With the benefits of real-time microbial monitoring seemingly clear, why is pharma hesitating?

The top two concerns regarding rapid microbial detection identified in our survey — high technology costs and regulatory concerns — come as no surprise, as they have been long-standing barriers to adoption. (Exhibit 7)

One third of those surveyed noted regulatory concerns about adopting new technology. Yet, the regulatory tides have definitely turned when it comes to at-line or on-line microbial monitoring. For

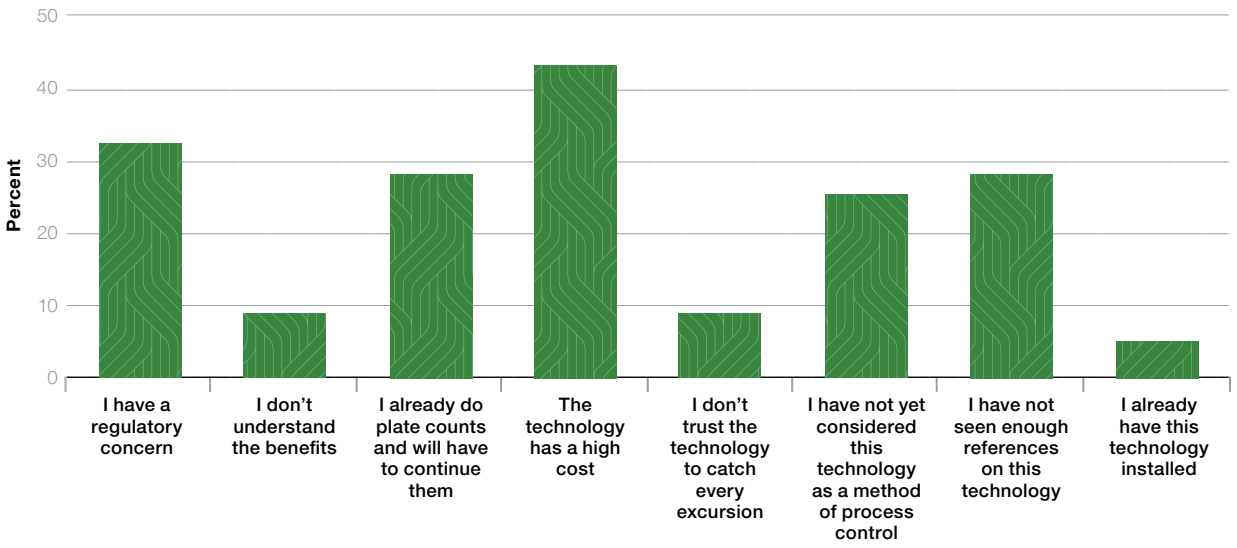

EXHIBIT 7

If you do not use this technology, or are assessing it, which of the following statements best describes your current situation

several years, the U.S. FDA as well as the European Medicines Agency (EMA) have pushed a process analytical technology (PAT) initiative. PAT involves the use of analytical instrumentation to monitor and control processes in real time, to allow changes and improvements to also be made in real time.

At industry events, the FDA has strongly endorsed on-line microbial instrumentation as a process control tool, including at recent Parenteral Drug Association meetings. The agency believes that these tools, when used in conjunction with traditional methods (such as grab sample plate counting), can significantly increase pharma's level of process control.

But the number one industry concern about rapid microbial detection, noted by 44% of respondents, is the high cost of technology. While installation of on-line or at-line methods does represent an upfront cost, the total cost of *not* installing such technology must be taken into consideration.

The use of real-time microbial monitoring technology in conjunction with the traditional plate counting needed to meet global compendial requirements reduces risk by providing a second data point. Manufacturers can react to excursions in real time, leading to faster and less costly resolutions.

Pharma manufacturers who have already adopted this hybrid approach have likely done so because they have unlocked the true value of real-time microbial monitoring technology. By moving beyond 100+ year old methods, they are experiencing less expensive microbial investigations and less investigations overall — and most importantly, new technology has empowered them to create safer pharmaceutical products. ◻