SARTORIUS

Addressing the Challenges of Quality Control Labs in Vaccine Manufacturing

November 1, 2021

Different vaccines types against COVID-19 are currently being manufactured and offered to the global population. Besides the mRNA vaccines which are completely chemically synthesized, the viral vector, inactivated and recombinant protein (sub-unit) vaccines are produced using cell culture-based manufacturing processes.

To ensure the safety, efficacy and quality of these vaccines a meaningful combination of measures need to be in place that comply with the principles of good manufacturing practices, including proving the consistency of the manufacturing process and testing for quality.

Addressing the Challenges of Quality Control Labs in Vaccine Manufacturing

As is the case with other biopharmaceutical products, the quality control (QC) of vaccines relies on three key components: control of the starting materials, control of the production process and control of the final product. This poses significant challenges to quality control labs in terms of time and sample testing requirements; it is estimated that about 70% of the production time of a vaccine is dedicated to quality control.

Testing for microbial contaminations throughout the manufacturing process is key to ensure the safety of the patients.

Human, animal and insect cells are commonly used in culture-based manufacturing processes and are typically susceptible to mycoplasma infections. Mycoplasma belong to the smallest known bacteria. They lack a cell wall and as a result can take on a very dynamic shape or form. If they enter the process, they can negatively impact the cultured cells and subsequently the product. This is manifested in alterations in the cell growth rates and morphologies, product yields as well as in DNA, RNA and protein synthesis. Testing for Mycoplasma is therefore necessary for the biologically derived raw materials and cell banks and each batch of the unprocessed bulk material (prior to harvest of the production bioreactor).

The traditional culture-based method challenges quality control in two ways. Firstly, viable but non-culturable (VBNC) Mycoplasma can go undetected when using the traditional method of mycoplasma cultivation, risking false-negative results. Secondly, a minimum of four weeks incubation time is required to be able to detect the presence of mycoplasma with certainty. It is especially challenging in continuous manufacturing processes where the bioreactor harvest can often not be held back too long; as a result, the process typically proceeds without Mycoplasma test results.

Sartorius' Microsart® qPCR kit offers a rapid solution for the early detection of Mycoplasma contamination. These kits are fast, highly specific, sensitive, and compliant with international guidelines. Alternative testing methods such as real-time PCR are gaining increasing acceptance by regulators with a need for a faster time-to-result when compared to traditional or compendial testing.

Microbial enumeration (bioburden) testing is another in-process quality control measure to demonstrate the safety and performance of the manufacturing process. In cell culture-based manufacturing processes it is required at the following stages:

- Raw materials (biologically derived)
- Cell banks (Master Cell Bank, Working Cell Bank)
- Unprocessed Bulk Material (prior to bioreactor harvest)
- Appropriate stages in the downstream process
- Drug substance

Membrane filtration is the regulatory-preferred method for microbial enumeration testing of liquids. However, handling a large amount of test sample materials including transferring the membrane filter to the microbiological growth medium is one of the most common sources of secondary contamination and false-positive results. Simple but effective – as often smart solutions can make a difference to daily routine tasks and simplify workflow steps. The Microsart® @filter combined with the Microsart® @media is a unique system which effortlessly positions the membrane on an agar plate completely touch-free. With only a turn of the lid, it's locked and ready to incubate, reducing the risk of contamination.

Alternatively, a rapid PCR-based total bacteria and fungi test can provide a quick result within 3 hours.

At the end of the process and as an essential product release parameter, sterility testing ensures that viable microorganisms are not present as contaminants in the final parenteral products, as most vaccines are administered as injectables.

Membrane filtration is the prescribed pharmacopeial method for sterility testing, the chapters USP<71> and the Ph. Eur. 2.6.1 specify that the 'technique of membrane filtration is used whenever the nature of the product permits'. Its advantage is that by filtering large volumes of a sterile product, even a single CFU (colony forming unit) in large volumes, perhaps litres, can effectively be retained on the membrane filter and subsequently cultured. The method also permits for the elimination of compounds with bacteriostatic or fungistatic properties through filtration and rinsing.

Rapid methods, as previously described, are gaining acceptance for the testing of short-shelf life products, such as cell and gene therapies as well as ATMPs and radiotracers used in PETs, and may also be used for traditional sterile pharmaceuticals. The Sterisart® device enables aseptic sampling during incubation by means of a septum port in the canister, ensuring compliance with global regulations. Product samples are filtered, the canisters filled with growth media and incubated for a period of 5-6 days. A sample is then drawn aseptically via the septum port and transferred to the rapid testing platform Celsis® (Charles River) for testing. This way quality control labs can maintain a growth-based strategy and at the same time achieve an earlier result. Further, the filtration method ensures that only viable microorganisms are reliably detected, avoiding any undue concern on background or noise, leading to false positives.

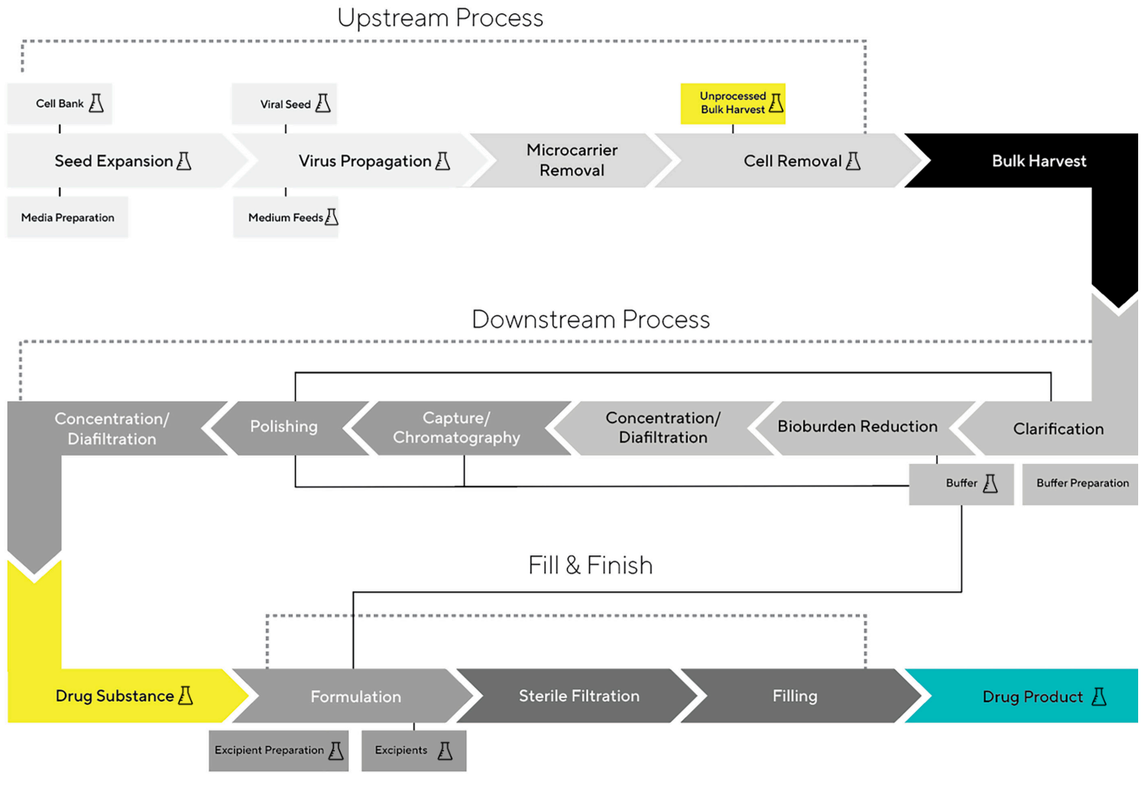
There are multiple sources of potential microbial contamination in any manufacturing process and cell culture-based processes are no exception. In sterile pharmaceutical production environments, the monitoring of the air is a key requirement and part of biocontamination control strategies as described in related standards and guidelines, such as the EN 17141 and the recently revised EU GMP Annex 1. According to the EU GMP Annex 1 Revision, continuous viable air monitoring has to be ensured during the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations and any risk caused by the intervention of the monitoring process should be avoided.

To comply with the need for long-term sampling, gelatin membrane filters are the optimal solution, and can be used non-stop for the whole production run, e.g. for 8h using only one single filter.

The MD8 Airscan® command unit utilizes a single, sterile gelatin membrane filter to capture and retain even the smallest airborne microorganisms, even viruses, over an 8 hour period. This USP-approved membrane filter can then be placed on any standard agar plate for routine incubation as per environmental monitoring protocols. This method of continuous active air monitoring keeps quality control labs compliant and avoids the risk of false positive results due to sampling errors.

In addition to microbial contaminations, other process-related impurities such us residual host cell proteins (HCP), produced during cell culturing and residual protein A (RPA) can also); a potential product purification contaminant can negatively impact the safety and efficacy of the vaccines produced in living cells. Therefore, these tests need to be included before in the final release testing package. Quality control labs typically use the Octet® Bio-Layer Interferometry (BLI) platform for such impurity lot-release assays. The Octet® system is also heavily used for other QC assessments including vaccine potency assessment through ligand binding assays, as well as to develop stability indicating methods that assess changes in activity through stressed and forced degradation assays. This easy to use platform helps the daily routine work of quality control technicians, and in combination with the high-throughput capability it enhances productivity.

Quality control testing is applied at several testing points (🧪) along the manufacturing process. Take a look at a typical cell-based vaccine manufacturing process and see where our products and services can help you overcome your quality control challenge.



For more information, please visit
www.sartorius.com

Germany
Sartorius Lab Instruments GmbH & Co. KG
Otto-Brenner-Strasse 20
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Corporation
565 Johnson Avenue
Bohemia, NY 11716
Phone +1 631 254 4249
Toll-free +1 800 635 2906

For further contacts, visit
www.sartorius.com