Application Note

PENDOTECH
Leading Process Analytics

Enhancing Recombinant Vaccine Production

With Single-Use Sensors

The production of recombinant vaccines involves crucial processes and faces various challenges linked to recombinant DNA technology, especially during the critical cell harvest phase. This stage includes separating and purifying target antigens from genetically modified host cells through methods such as centrifugation, filtration, and advanced purification techniques. Additionally, UV absorbance measurement plays a vital role in monitoring the concentration and purity of the target antigens during purification. The importance of effective monitoring and control of other key parameters—temperature, pH, conductivity, and pressure—is highlighted as essential for ensuring product quality and safety during downstream processing.

Background

Recombinant vaccines are developed using recombinant DNA technology, which involves inserting DNA that encodes an antigen from a pathogen into a host cell. This prompts the cell to produce the antigen in large quantities, after which the antigens are purified and formulated into the vaccine [1]. Such vaccines are generally considered very safe because they do not use live pathogens and can be designed to exclude harmful components, which allows them to elicit a strong immune response. Additionally, they can be produced quickly and in large quantities, making them especially useful during pandemics. The technology also enables precise targeting of specific antigens, enhancing a vaccine's specificity.

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Process

The cell harvest step in recombinant vaccine manufacturing is crucial for ensuring the quality and safety of the final product. This step involves a series of precise processes to separate and purify the desired antigen from genetically modified host cells [2]. Initially, the host cells are cultured to produce the target antigen, and once sufficient levels are achieved, the culture medium is processed to separate the cells from the medium. This separation is primarily accomplished through centrifugation, which utilizes density differences, and various filtration methods, including depth filtration to remove larger particles and tangential flow filtration (TFF) for further refinement. After the initial separation, intermediate purification techniques such as ultrafiltration and diafiltration are employed to concentrate the product and eliminate smaller impurities, enhancing the purity of the final output. Following these processes, additional purification steps are taken to isolate and concentrate the antigen effectively, ensuring it is free from host cell contaminants and other impurities. Throughout this entire process, rigorous monitoring and control are essential to assess the efficiency of each step, ultimately ensuring that the produced antigen meets the necessary quality and safety standards for vaccine formulation. By maintaining meticulous control over the cell harvest stage, manufacturers can achieve a high-purity antigen or virus critical for developing effective vaccines, ensuring the final formulation is safe and efficacious for its intended use.

Controlling parameters in downstream processing during vaccine manufacturing is essential for ensuring the quality and safety of the final product, and requires attention to several significant factors. Maintaining process consistency is a major concern, as stable conditions such as temperature and pH are crucial for protein stability, while conductivity facilitates efficient buffer exchange. Monitoring pressure in chromatographic columns and filtration systems is vital for optimal performance, and UV absorbance sensors accurately determine protein concentration. Additionally, turbidity measurements play a critical role in detecting filter breakthrough and indicating the presence of microbial contaminants. Effective management of these aspects necessitates rigorous monitoring and control systems to uphold the integrity of the manufacturing process, ultimately resulting in the production of safe and high-quality vaccines. Contamination control is also vital, as preventing microbial presence demands stringent management of environmental conditions and thorough testing protocols, since any contaminants can compromise product integrity. Implementing single-use, in-line, real-time monitoring systems to continuously track control parameters is crucial for maintaining process control and product quality. Moreover, automating these controls enhances consistency and reduces human error, ultimately improving the efficacy and reliability of vaccine manufacturing processes.

Switching from traditional systems to single-use systems in biopharmaceutical manufacturing brings several advantages that boost both operational efficiency and product safety. Single-use systems significantly reduce the risk of cross-contamination between batches, which is crucial for maintaining purity in biopharma production [3]. They also reduce cleaning requirements, eliminating extensive cleaning and validation processes that can lead to downtime and increased labor costs. Additionally, single-use technologies enhance flexibility by enabling quicker changeovers between products. This adaptability not only streamlines operations but also facilitates easier scaling according to varying demand, ensuring that production processes remain efficient and responsive. Furthermore, these systems streamline operations by being pre-sterilized and ready for use, often require less physical space, and can enhance process control through built-in sensors and monitoring capabilities. Combined, these benefits contribute to a faster time to market and a more agile response to evolving market demands.

Challenges

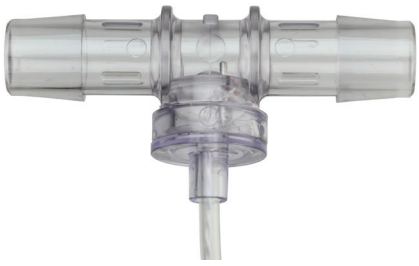
The purification of antigens involves multiple steps, including centrifugation, filtration, chromatography, ultrafiltration, and diafiltration. Each step must be optimized to ensure maximum yield and purity. Balancing the efficiency of these purification techniques while minimizing losses is challenging [4].

conductivity, and pressure. Inconsistencies in these measurements can compromise the efficiency of the chromatography, UF/DF, depth filtration, viral inactivation and packaging steps. Fluctuations in these parameters can adversely affect protein stability, which in turn impacts the yield and functionality of the produced antigen and ultimately affecting the purity and safety of the final product. To address these challenges, manufacturers need to establish comprehensive monitoring and control systems that facilitate real-time tracking and adjustment of these parameters. This includes use of precalibrated, presterilized single-use sensors to maintain accurate readings and integrating automated solutions to minimize human error, ensuring that the production process remains efficient and reliable.

METTLER TOLEDO Pendotech Solutions

Temperature sensor

METTLER TOLEDO Pendotech Single Use Temperature Sensors offer accurate temperature measurement for processes requiring single-use applications to prevent cross-contamination while also being robust enough for repeated cleaning. Designed for in-line use, they are ideal for filtration, chromatography, filling operations, and general monitoring. These sensors are compatible with a range of monitors, including Pendotech's TEMP-340 handheld unit, and pre-qualified third-party devices, featuring reusable cables for easy connection. Available with hose-barb fittings, a 1-inch sanitary flange, or a luer fitting, the sensors ensure no obstruction in the fluid path and require no calibration due to the well-defined temperature versus resistance characteristics of the thermistor element. With high sensitivity and accuracy of better than ±0.2°C (typically better than ±0.1°C) within the 0-70°C range, the sensors are constructed from polysulfone for hose-barb and flange types and polycarbonate for luer fittings, all meeting USP Class VI requirements and manufactured in an FDA Registered, ISO 9001 certified facility, and include a certificate of quality.



pH sensor

Single-Use In-line pH Sensors from METTLER TOLEDO Pendotech are equipped with advanced InSUS 307 pH probe technology, delivering accurate and reliable pH measurements in downstream bioprocessing operations. These sensors are designed to perform with great precision within the pH range of 3 to 10, with an accuracy of ± 0.10 pH when operating within ± 1.50 pH units of the 1-point process calibration point. With a quick response time of under 20 seconds between pH 4 and 7, they can capture rapid pH shifts due to process changes. The InSUS 307 pH sensors are also rated for a temperature range of 5-60°C and a pressure range of 4 bar at 25°C, 2 bar at 40°C, and 1 bar at 60°C, making them a highly versatile and effective choice for bioprocessing operations.

Conductivity sensor

Our Single-Use Conductivity Sensors™ and Conductivity Monitor are an ideal choice for organizations seeking for highly accurate conductivity and temperature measurements without requiring sensor calibration. The monitor features automatic temperature compensation that normalizes conductivity readings to 25°C. 4-20mA outputs are available for both conductivity and temperature to transmit the readings to a higher-level control system, such as a PLC or DCS. An RS-232 output also enables data collection on a PC. These sensors are designed for conductivity measurement in the range of 0.1 to 100mS/cm and process temperature in the range of 2°C to 50°C.

With this wide range of measurement capabilities, these sensors can optimize your bioprocess, making it more efficient and productive.

Pressure sensor

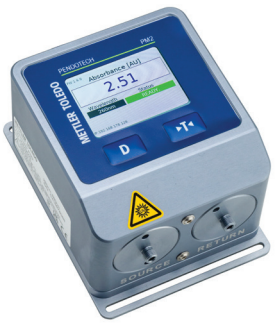
METTLER TOLEDO Pendotech's Single-Use Pressure Sensors provide precise measurements of static and dynamic pressure for gases and liquids in biopharmaceutical processes. These sensors are ideal for disposable applications and are a reliable alternative to stainless steel pressure transducers.

The pressure sensors, equipped with High Accuracy Pressure (MEMS-HAP™) chips, are ideal for monitoring filtration, chromatography, and bioreactors. They come with hose-barb connections that range from 1/8 to 1 inch (3.175 mm - 25.4 mm), as well as sanitary flange and luer connections. Designed for repeated cleaning and re-use, these sensors operate within a pressure range of -11.5 to 75 psi (-0.79 to 5.2 bar). Their clear flow path and absence of dead legs result in reduced hold-up volume compared to traditional stainless steel transducers or gauges. The sensors have varying accuracy levels based on the pressure being measured: ±2% for readings from 0 to 6 psi, ±3% for 6 to 30 psi, and ±5% for 30 to 60 psi.

Made from either polycarbonate or caustic-resistant polysulfone, all materials in the fluid path comply with USP Class VI requirements both before and after irradiation. Each lot includes a Certificate of Quality, and individual NIST Certificates can be requested. The sensors are manufactured in an ISO 9001 certified facility with an ISO Class 7 clean room and are compatible with gamma and X-ray irradiation. Additionally, they feature a test port for non-invasive testing in place.

UV-Vis absorbance sensor

The photometer is a highly adaptable instrument designed for use in both laboratory and process settings, available in both benchtop and panel mount versions. It boasts factory configuration with seven different wavelength combinations, making it easy to integrate into a monitor with data acquisition capabilities. Equipped with two 4-20mA output signals and a local display, it allows for easy reading and viewing. The photometer is compatible with a variety of data acquisition devices and control systems and supports digital communication protocols. Its non-invasive, real-time measurement of UV absorbance enables reliable identification of the presence or absence of a target molecule, while its ability to monitor concentration changes and detect absorbance peaks enhances its utility. The photometer also offers a low-cost solution for single-use applications, with flow cells that can be repeatedly cleaned and reused. Furthermore, it supports a range of flow cell sizes and path lengths to accommodate different applications and process scales.



Conclusion

Enhancing recombinant vaccine production through the adoption of single-use sensors presents a transformative approach to overcoming the challenges associated with traditional manufacturing methods. The critical cell harvest phase, which involves meticulous separation and purification of target antigens, can significantly benefit from the integration of real-time monitoring technologies that ensure optimal control of key process parameters such as temperature, pH, conductivity, and pressure. By implementing single-use systems, manufacturers can significantly reduce the risk of cross-contamination, streamline operations, and enhance product quality while minimizing cleaning and validation requirements. Moreover, the flexibility and efficiency afforded by these single-use sensors facilitate rapid responses to changing demands in vaccine production, ensuring that high-purity antigens are consistently achieved. Ultimately, leveraging advanced single-use technologies not only enhances the safety and efficacy of vaccine formulations but also accelerates the time to market, making it a crucial strategy in the ongoing pursuit of effective biopharmaceutical manufacturing.

References

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METTLER TOLEDO Group
Process Analytics
Local contact: www.pendotech.com

www.pendotech.com
For more information

PA4174 en A
MarCom Plainsboro, USA