Jansen Communications
Public Relations & Marketing

Monitoring Critical Process Parameters in Upstream Processes

Hamilton Bonaduz AG offers comprehensive in-line sensor portfolio

Manufacturing biopharmaceuticals is not only a costly, but also, due to their origin of living cells, a highly complex and time-consuming process. The cells' heterogeneity and sensitivity regarding chemical influences, such as changes of the pH value, require a profound process understanding. Even little changes of process parameters may influence the yield and quality of the target molecule positively or negatively. That being said explains why identification and continuous monitoring of critical process parameters is important.

Detecting critical quality attributes and process parameters

Cultivation of sensitive organisms in biotechnological processes can be improved, analyzed and controlled best using process analytics technologies (PAT). The principle is based on profound understanding of science and technology as well as on identifying the variables that influence quality and quantity of target molecules. The goal is to monitor the quality attributes and process parameters with continuous measurements in order to ensure the quality of the final product. PAT puts emphasis on process understanding ra-

ther than on the product itself. The explanation is simple: the quality of the final product is secured, if the process is understood in the first place. So first of all, the critical quality attributes and process parameters that may vary depending on the culture or target molecule are identified. In this way, the determined optimal process conditions can be set and monitored accordingly within defined limits. This is an important step for the commercial success of the upstream process, in which cells, yeast and bacteria grow gradually. Critical process parameters, such as pH value, dissolved oxygen, but also cell growth, should be determined continuously and consequently in-line.

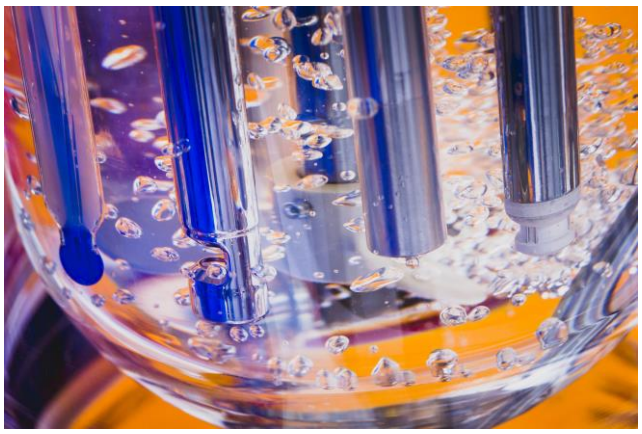
Monitoring pH value, dissolved oxygen and cell growth

Cells of different origins are characterized by different optimal pH values. The ideal pH value for animal cells is mostly between 6.8 and 7.4, whereas the pH value for insect cells is slightly lower at about 6.3. If the pH value is not at or close to ideal, cell growth and yield of the desired target molecule might get affected negatively. Therefore, the use of pH sensors in media preparation and during cultivation is very common. The pH sensors of the EasyFerm Plus family are compatible with all common controllers and process control systems. The EasyFerm Plus family is especially suitable for all upstream process steps, due to their robust design, high measurement accuracy and reproducibility. Another important process parameter is the dissolved oxygen content. The desired dissolved oxygen saturation can easily be monitored with the optical dissolved oxygen sensor VisiFerm DO. Due to the optical measurement principle, VisiFerm DO needs neither polarization nor electrolyte refill, unlike the traditional Clark sensors. Additionally, the measurement is not influenced by the metabolism by-product CO2 causing changes of the pH value of the electrolyte. Conditions for an ideal cell growth are ensured by monitoring and adjusting optimal values for pH and dissolved oxygen saturation. Whether this is successful and cells grow as expected can be tracked via in-situ measurement of the viable cell density. The Incyte sensor measures permittivity by only polarizing viable

cells within an alternating electrical field. An increasing permittivity correlates with growing cell numbers, which can be calculated after preparing a cell type-dependent calibration curve. Conclusions about the nutrient supply and the subsequent yield of the target molecule can be drawn by means of continuous permittivity measurement.

Conductivity measurement of great importance

The quality of the water used in an upstream process is very important for its success. This applies to the water used for the production of the culture media as well as to the water used for cleaning and rinsing purposes. Compliance with the strict requirements for ultra-pure water defined by the pharmacopeias EP and USP is crucial. One of the most important parameters is conductivity measurement. The conductivity sensor Conducell UPW (Ultra-Pure Water) measures low conductivities reliably and complies with the requirements of legal pharmacopeias. The principle is based on the measurement of the electrical resistance via a 2-pol sensor. As required in the mentioned pharmacopeias, warnings can be issued at increased conductivity, so that corrective measures can be taken.



Sensor calibration under defined conditions

All mentioned sensor types are available in the Arc version. This means that an off-line calibration under defined conditions can be conducted in a laboratory, since the micro-transmitter in the sensor head stores all calibration data. With the help of an optional wireless adapter, measurement values and sensor information can be sent via Bluetooth to a mobile device. The Arc version allows in this way to adjust sensor configuration and calibration in-situ, and to determine and resolve the cause of a malfunction. A robust sig-

nal, either 4-20 mA or Modbus, are further characteristics of the Arc technology to ensure smooth and seamless processes.

Critical process parameters are monitored in real-time with the help of in-line sensors and the implementation of PAT in bioprocesses. The acquired data provide important insights into the process and go along with improved efficiency and reliability.