IN-LINE MONITORING AND CONTROL OF GLUCOSE CONCENTRATION WITH SINGLE-USE SENSORS IN CHO AND STEM CELL APPLICATIONS

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Nearly 20 years ago, the Food and Drug Administration (FDA) published a guidance document to describe a regulatory framework for process analytical technologies and to promote innovation in pharmaceutical development, manufacturing, and quality assurance [1], in which process analysis and control tools play an important role. Since then, the capabilities for on-line, at-line, and in-line measurement of various parameters have continuously evolved.

One of the most critical parameters in mammalian and stem cell cultivation is glucose, the most important carbon source, alongside pH and dissolved oxygen, which are already measured and controlled in-line in many bioreactors. While high glucose levels can be inhibitory, limitation rapidly leads to apoptosis in most cell types. In this work, CITSens Bio sensors (C-CIT Sensors AG) were used for in-line measurement of glucose in T25-flasks during hASC expansion (ASC52telo, ATCC) in a serum- and xeno-free stem cell culture medium (UrSuppe [2-3]). The hASC expansion process ran for 6 days in batch mode. The glucose concentration measured in-line was in good agreement with the measurements determined off-line (Cedex Bio, Roche).

In further experimental runs, the sensor was used for the automated control of the glucose concentration in a fed-batch IgG production process with CHO suspension cells (ExpiCHO-S, Gibco). For this purpose, a glucose solution was pumped into the stirred bioreactor (2 L working volume) in addition to a continuous supply of feed solution, in order to constantly regulate the concentration to a minimum of 1 g/L. The glucose concentration was successfully measured throughout the 21-day process and regulated to values between 1.12 g/L and 1.38 g/L from day 8 to day 21 of the cultivation. The IgG titer achieved in this automated fed-batch process was 3.7 g/L, comparable to the conventional processes using a daily bolus feeding.

References

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