EFFECTIVE CELL CULTURE OPERATIONS BY IMPLEMENTING ACCURATE, NON-INVASIVE DETERMINATION OF THE CRITICAL PROCESS PARAMETER pH IN ROCHE`S DRUG SUBSTANCE NETWORK

Christian Klinger, Roche Diagnostics GmbH, Germany
mailto: christian.klinger@roche.com

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In mammalian cell culture, especially in pharmaceutical manufacturing, pH is a critical process parameter that must be controlled as accurately as possible. Not only is pH directly affecting cell culture performance. Ensuring a comparable pH is also crucial for scaling and transfer of cell culture processes. Sample-based offline pH measurement thereby ensures correct bioreactor pH probe signals after sterilization and as a detection measure for drifts of probe signals. However, accuracy and precision of sample-based offline pH is limited. Offsets between bioreactor pH and sample pH heavily depend on equipment, local procedures, sample properties and the offline measurement method that is used.

Limited accuracy and precision of pH thereby undermines efforts to efficiently scale and transfer and massively contributes to unintended process variability in Development and within manufacturing campaigns. This increases the number of deviations leading to difficult root cause analysis. Additionally, post-harvest fluids may have variable properties for downstream processing regarding product concentration, quality and impurities. Process variability in general severely affects the information contained in the data generated, limiting success of efforts in the field of data science.

Extensive efforts to quantify accuracy of sample based offline measurement have been undertaken. Results presented highlight a best-case accuracy of around +/- 0.1 pH. Roche did therefore develop and implement a method to determine pH accurately and precisely without having to sample. This method relies on offgas measurement and utilizes the relationship of carbon dioxide in the gas phase and corresponding pH in the liquid phase of a bioreactor. The relationship of carbon dioxide and pH is naturally independent of scale and local procedures. This means an accurate and reliable reference is available to establish and prove pH comparability cross-site and scale.

The method is already established as a standard in Research, Clinical, Development and commercial manufacturing. Current initiatives expand utilization of the method as a global standard within the Roche Drug Substance Network.

We will present limitations of sample based offline measurement for pH and how the non-invasive, offgas based method benefits Roche`s cell culture operations.

We firmly believe this method to be a potential new industry standard providing accurate, precise and robust pH from clone identification up to commercial manufacturing. Furthermore, better data with less unintended variability and error allows for more efficient detection and quantification of other effectors onto cell culture performance like raw materials, seed train and inoculum train operations amongst others. This will in the end lead to more efficient processes overall, contributing to Roche`s Pharma vision of more patient benefit at less cost to society.