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METHOD DEVELOPMENT, VALIDATION, AND IMPLEMENTATION OF RAMAN SPECTROSCOPY AS AN IN-SITU PROCESS ANALYTICAL TECHNOLOGY FOR FERMENTATION PROCESS DEVELOPMENT AND COMMERCIAL MANUFACTURING

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Microbial fermentation processes are widely used in industry as production methods for the development and manufacture of numerous vaccine candidates. The rapid nature of some microbial fermentations renders both quantitative and qualitative process analytics challenging. Glucose, a carbon source necessary to drive fermentation metabolism, is a common analyte of interest for quantification throughout a fermentation process. Traditional off-line analysis methods for metabolites such as glucose consume valuable time, require costly resources, and present unnecessary hazards to personnel when working with pathogenic organisms. The necessity for a robust and in-situ analytical method capable of delivering real-time measurements was evident. Here we discuss the successful method development, validation, and implementation of Raman spectroscopy as an in-situ Process Analytical Technology (PAT) for glucose quantification during process development and commercial scale fermentations. Utilizing the Kaiser Raman system with a 785nm laser, raw spectral data was collected throughout fermentation batches in bioreactors, pre-processed, and correlated to off-line glucose reference data. Using chemometric techniques and multivariate analysis, a Partial Least Squares (PLS) model was created to yield real-time and accurate glucose predictions. Through this work, the Raman PAT glucose method was validated for commercial use to improve process robustness, reduce operating costs, and limit off-line sample manipulations. The value and feasibility of Raman spectroscopy as an in-situ PAT method is demonstrated and recognized as an enabling technology suited to mitigate several challenges fundamental to vaccine process development and commercial manufacturing.