IMPLEMENTATION OF PAT-BASED CONTROL STRATEGY FOR CONTINUOUS FORMULATION

Sushmitha Krishnan, Sanofi, USA
sushmitha.krishnan@sanofi.com
Shashi Malladi, Sanofi, USA
Erin Holahan, Sanofi, USA
Chad Varner, Sanofi, USA
Michael Coolbaugh, Sanofi, USA
Marina Hincapie, Sanofi, USA
Jason Walther, Sanofi, USA
Kevin Brower, Sanofi, USA

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Much of the focus in continuous bioprocesses has been on chromatography and, more recently, filtration, yet developing the approach for final formulation is key to a complete end-to-end process. As the last step in purification, the formulation operation presents unique challenges due to (1) high product concentrations in the process stream following UFDF, making accurate in-line measurements difficult, and (2) approximately 10x lower flow rates in this step compared to upstream operations, resulting in challenges to reliably measure process flows. This work aims to describe control strategies developed and applied to continuous final formulation to address these challenges, leading to significantly improved consistency in formulated drug substance (FDS) generation.

Robust formulation requires excipient addition at constant proportions to the product stream and concentration adjustment in response to dynamic UF outputs. In a batch operation, these additions are performed using volume or weight-based approaches, adding these components typically at 5-10% of the bulk product. Although volumetric methods using flow rates are most analogous to batch formulation, previous attempts using this approach for continuous processing resulted in >20% variation of concentration and osmolality in the FDS. This variation is exacerbated during low flow operation, where accuracy of bioprocess-compatible flowmeters significantly decreases.

We have developed a novel methodology in which key quality attributes were measured in-line in real-time using various PAT tools. These measurements served as inputs to a control strategy using a unique combination of feedback, feed-forward, and additional complementary controls. This approach enabled operation that was robust to perturbations in feed flow rate and concentration, allowing finer control over simpler approaches alone. In this work, we will present the PAT tool selection process to accurately measure key attributes, the details of the control logic, and the controller performance as measured in FDS both online and offline. Ultimately, this control strategy was implemented in a continuous commercial-scale operation which resulted in FDS generated with <5% variation in concentration and osmolality over a 6 day, hands-off operation, thus generating drug substance lots with significantly greater consistency than previously observed. Through this approach, we can overcome the challenges of low flow, high concentration regimes and ensure scalable and robust operation of a fully end-to-end continuous process.