CHARACTERIZATION AND CONTROL OF CULTURE MEDIA AND BUFFER PREPARATION PROCESSES: CLOSING THE GAP

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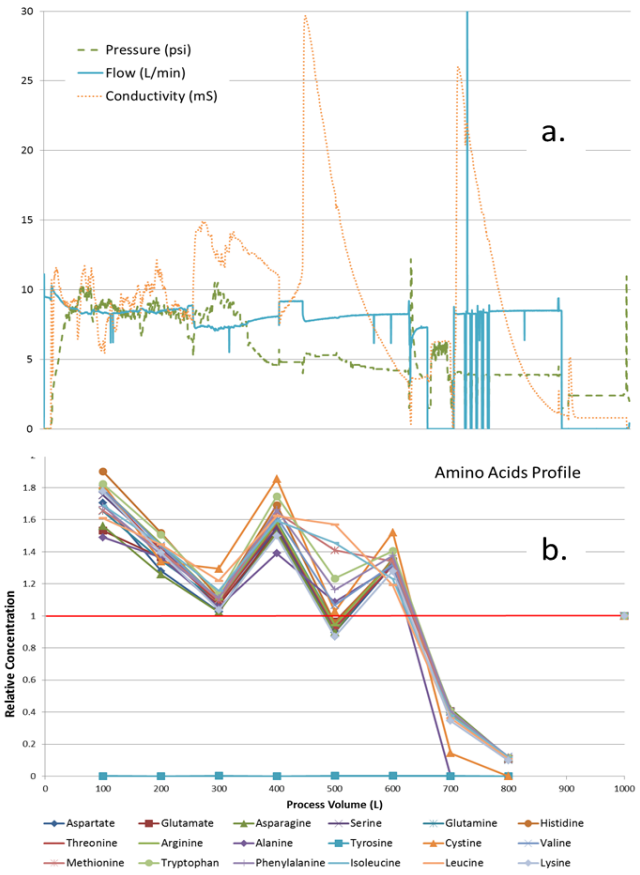
As supporting processes, culture media and buffer preparation add little direct value to the biopharmaceutical bulk drug substance manufacturing process. However, these necessary unit operations represent an inordinate amount of risk to an overall process both in terms of potential for contamination (Fletcher and Harris, 2016) and potential for introducing variability. For these reasons, media and buffer preparation represent an untapped opportunity for optimization and reducing risk. Closing this gap would mean eliminating one of the last remaining weak links in the vision of building a closed manufacturing process. A case study for applying novel technology that provides real-time process monitoring and control of these processes is described here. An automated system has been designed to deliver sterile process solutions from single-use cartridges of premeasured raw materials. Featuring in-line sensors and controls as part of the functionally-closed system provides opportunity to improve characterization and control. Because they provide more complete batch records, better control and better traceability of the process, these improvements are valuable for both development and manufacturing and facilitate a more seamless scale-up from pilot to commercial scale. Since the technology described provides opportunity for making these processes more data-driven, it also provides opportunity for them to be optimized using methods common for other unit operations. Process analytical tools can be applied and the related benefits realized.



Figures. a) Real-time process monitoring and control, b) Amino acids profile

Traditional media and buffer preparation processes using single-use mixers or stainless steel mixing tanks capture at most one of the three requirements expected by facilities of the future: 1) a functionally-closed process, with 2) cost-effective, seamless scale-up, and 3) a fully traceable and controlled design space. Meeting all three requirements is necessary in order to physically, economically, and conceptually close some of the last gaps in building a complete end-to-end manufacturing process.

An in-line, single-use device has been developed that effectively extends functionally closed, integrated processes one step further upstream to include the media and buffer preparation process. In addition to all the general advantages of employing single-use methods (reduced risk of cross-contamination, reduced cleaning costs, reduced capital expense, reduced time for setup or re-configuration), this new approach offers several unique advantages over conventional methods. Several complete, chemically defined, dry powder media and buffer formulations have been used to develop and prove the device up to 1,000L scale. As bioprocesses are being intensified to deliver greater volumetric productivities, and facilities are being designed to be ever smaller and more efficient, sterile media and buffer preparation have been identified as unit operations that offer significant opportunities for improvement.

References

T. Fletcher, H. Harris., Safety drives innovation in cell-culture media technology. *BioPharm International*. Vol. 29, No. 9, pg 22–27 (2016)