Accelerating process development for biologics on an automated, pharmacy-scale manufacturing system

by

Laura E. Crowell

Department of Chemical Engineering

Research Advisor: J. Christopher Love

Thesis Committee Members: Charles Cooney, Steven Cramer, Douglas Lauffenburger

Technical Summary

The conventional large-scale, centralized, single-product manufacturing model for biologic medicines does not allow for the economical production of drugs for small patient populations or for the distribution of these drugs in developing countries. A decentralized model featuring small-scale, fully automated, multi-product manufacturing of biologics at the point-of-care could address some of these issues. To truly realize the benefits of such a manufacturing paradigm, it must also be paired with rapid process development methods for the production of new products. In this thesis, we describe the development of a bench-scale, automated, multi-product manufacturing system for the end-to-end production of hundreds to thousands of doses of clinical-quality protein medicines in about three days. We then demonstrate the application of this platform to the manufacture of a trivalent vaccine in a single campaign through co-expression and co-purification. We further demonstrate new methodologies for the accelerated development of manufacturing processes to produce new molecules on the system, including a strategy for the development and optimization of fully integrated, multi-column processes for straight-through chromatographic purification, and the development of a platform process for the production and purification of single domain antibodies. We then propose a workflow for the collection of a dataset relating the chromatographic behavior of host-cell proteins to their biophysical characteristics with the goal of building an *in silico* tool for the prediction of purification processes for any new molecule. Finally, we propose a platform approach, as opposed to a platform process, for the development of manufacturing processes for new biologics. This platform approach utilizes tools intended to gain a deeper understanding of common process development challenges with regard to the host and to the molecule itself. Ultimately, we believe that the combination of a small-scale, automated manufacturing platform and accelerated strategies for developing processes to manufacture new products on the platform could enable time- and cost-efficient manufacturing of a wide variety of biologic drugs, increasing access to medicines throughout the world.