Title: Decision Support System for Improved Scheduling, Maintenance, and Assessment of Biopharmaceutical Processes

Name: VAIBHAV KUMAR

Entry Number: 2014CHZ8289

Abstract

Biopharmaceuticals are therapeutic drugs that successfully cure autoimmune diseases by manipulating patient genetics with fewer side effects than traditional chemical drugs. Under the risk of high clinical failure linked to drug development coupled with more significant process variability, designing a decision support system for multiproduct facilities in biopharmaceuticals remains a challenge. Computer-aided decision support systems have been used to assist decision-making in the past for biopharmaceutical processes using heuristic approaches for production planning and scheduling, facility design, debottlenecking, and capacity analysis. Much work has been done towards planning, scheduling, and optimization in process systems engineering (PSE), and recently increasing efforts are being made to understand process design and optimization in the biopharmaceutical industry. More work is required to get a more precise, deeper, and better understanding of process design and optimization in this field. Therefore, the purpose of the present study is to conduct research and develop novel models to fill the gap between computer-aided process design tools and mathematical optimization and scheduling.

The first objective in this thesis is to propose an extension of the earlier unit-specific event-based literature model to address the observed model inconsistencies such as early product delivery, no initial setup time, no proper mapping of upstream and downstream tasks, and storage sequencing. Then in the second part, an improved model is proposed with features such as minimum campaign length and shelf-life occurring over consecutive multiple events, modified material balances, sales and penalty constraints, and new initial setup sequencing constraints. Then it is extended for handling the early product delivery case by providing new material balance and sales and penalty constraints. The improved model gave better results compared to the literature.

Chromatography has a significant impact on the purity attributes of the final product in the bio-pharmaceutical industry. Limited lifetime and higher cost of chromatography resins make it necessary to get the maximum yield from the process step, due to which the resins are reused multiple times. Therefore, maintenance (i.e. restoring resin capability and performance to its initial level) is one of the most critical decisions for such processes. So, when to plan

the maintenance operation subject to performance decay is crucial in the bioprocess facility design and scheduling. In the second objective, a state task network (STN) framework-based, unit-specific event-based model is proposed for performance decay of chromatography resin for optimum resin utilization, which shows improvement in profit and capacity utilization over the literature models that used discrete events and global events.

The third objective is to conduct research and develop novel mathematical models to fill the gap between computer-aided process design tools such as SchedulePro® and mathematical optimization and scheduling. To explore techno-economic benefits, if any, some examples adopted from the SchedulePro® library on a microbial biopharmaceutical process are modeled and validated using mathematical programming-based approaches. Two unit-specific event-based models are proposed with and without utility constraints, which shows improvement over the heuristic approaches. In the fourth objective, the proposed mathematical model for batch processing is demonstrated on available experimental data for production of Lethal Toxin Neutralizing Factor (LTNF) and Granulocyte Colony-Stimulating Factor (GCSF).

Keywords: Optimization, Scheduling, Mathematical programming, Biopharmaceuticals, Shelf life, Storage.