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A shortcut approach for decision-making and operational analysis of an integrated end-to-end continuous pharmaceutical process

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To be submitted to PSE-2018

The pharmaceutical industry has traditionally been dominated by batch processing which has many inherent disadvantages, such as high costs and environmental footprint, long processing time and poor flexibility. Moreover, drug development is a complex, long and costly process, entrenched with high degrees of uncertainty regarding the success of the clinical trials and scale-up. To address some of these issues more effectively, the economic and regulatory drivers are more than ever pushing the pharmaceutical industry towards continuous manufacturing, which demonstrated tremendous advantages over batch processing. Integrated end-to-end continuous pharmaceutical manufacturing has particularly attracted a lot of interest over the last few years (Benyahia et al., 2012; Mascia et al., 2013; Cole et al., 2017). However, the integrated continuous approach can be very challenging and requires more rigorous and robust decision making tools for design, development and supply chain management, to meet the regulatory, economic, environmental and safety requirements. In pharmaceutical process development, the standard is to first develop different production scales to supply clinical trials. Afterwards, feasible and viable technologies for full production scale and operational windows are identified in a very short time during the post approval period, to be able to produce as long as possible while the API is still patent protected. These singularities make the pharmaceutical process design and development very challenging and several operational alternatives (within a fixed design space) need to be systematically evaluated during start-up, steady-state and non-routine process upsets (presence of disturbances).

In this work, a plant-wide model-based shortcut approach for decision-making and operational analysis of integrated end-to-end continuous pharmaceutical processes is developed and tested. The proposed hierarchical approach is implemented through a computer-aided framework. Concepts of Layer of Protection Analysis (LOPA) combined with Net Present Value (NPV) are embedded in the framework from a model-based point of view to comprehensively assess the overall benefits of a specific operational point, which in turn can be used to make an informed decision between competing operation alternatives. The application of the framework is demonstrated through a validated pilot-scale continuous pharmaceutical dynamic process model (Benyahia et al. 2012). In this application, the implications of changing process operations from single pass operation to raw material recycling have been investigated. It was first demonstrated that introducing process recycle will create a potential systematic saturation of impurities, which requires an increased purification as well as a reduced ability to reject non-routine process disturbances. The NPV value output from the comprehensive analysis conducted was then used to determine the most feasible operating condition between single pass operations, complete recycle and base case design recycle ratio (validated

previously by a pilot-scale continuous process). Results on the environmental footprint inherent to each scenario, evaluated in terms of its e-factor, are also reported.

The application of this shortcut approach can facilitate decision-making and reduce development costs through a rapid evaluation of process economics, environmental aspects and economics. In future, it is beneficial to include control strategy evaluations and recommendations for process analytical technology (PAT) as well.

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