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Discrete Event Simulation Modelling for Dynamic Decision Making in Biopharmaceutical Manufacturing

Madhu Sachidananda[a]*, John Erkoyuncu[a], Daniel Steenstra[a], Sandra Michalska[a]

[a]*Cranfield University, Cranfield MK43 0AL, United Kingdom*

* Corresponding author. Tel.: +44(0)1234 750111; *E-mail address:* m.sachidananda@cranfield.ac.uk

Abstract

With the increase in demand for biopharmaceutical products, industries have realised the need to scale up their manufacturing from laboratory-based processes to financially viable production processes. In this context, biopharmaceutical manufacturers are increasingly using simulation-based approaches to gain transparency of their current production system and to assist with designing improved systems. This paper discusses the application of Discrete Event Simulation (DES) and its ability to model the various scenarios for dynamic decision making in biopharmaceutical manufacturing sector. This paper further illustrates a methodology used to develop a simulation model for a biopharmaceutical company, which is considering several capital investments to improve its manufacturing processes. A simulation model for a subset of manufacturing activities was developed that facilitated 'what-if' scenario planning for a proposed process alternative. The simulation model of the proposed manufacturing process has shown significant improvement over the current process in terms of throughout time reduction, better resource utilisation, operating cost reduction, reduced bottlenecks etc. This visibility of the existing and proposed production system assisted the company in identifying the potential capital and efficiency gains from the investments therefore demonstrating that DES can be an effective tool for making more informed decisions. Furthermore, the paper also discusses the utilisation of DES models to develop a number of bespoke productivity improvement tools for the company.

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Keywords: Discrete Event Simulation; Biopharmaceutical Manufacturing; Dynamic Decision Making

1. Introduction

EvaluatePharma World Preview consensus forecasts the prescription drug sale to be $895 billion of which biological products account to about 50%. [1]. With this increasing demand, biopharmaceutical manufacturers are now looking at scaling up their manufacturing processes to mass produce biological products, especially Gene Therapy (GT) products. GT is a new generation of biopharmaceutical drugs that are targeted at treating genetic disorders as well as life threatening conditions such as cancer. FDA (2013) defines GT as a 'treatment process that introduces genetic material into a DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition' [2]. Despite their increasing popularity and promising nature, most of GT products have long remained in clinical trial phases. With the completion of clinical trials nearing the end, there is a definite possibility for these drugs to be developed into commercially available and effective GT products. However, unlike conventional drugs that are mass produced, GT products are novel/complex and hence offer unique challenges in product development. Complex manufacturing processes [3], high cost of production [4], high risk of clinical failure [5], strict regulatory policies [6] are likely to affect the manufacturing processes. GT companies considering expansion need to make investment decisions under these uncertain conditions and have to realise that the key to their commercial success lies in optimal planning, efficient manufacturing and early assessment of cost/benefits. Therefore, computer-aided simulation tools are increasingly being used to capture the dynamic behaviour of the current process and to experiment with various process alternatives.

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This paper presents a Discrete Event Simulation (DES) model developed in Witness 13 visualising a subset of the GT manufacturing processes in order to assess the impact of the proposed investment decision involving a process alternative. The model evaluates the alternatives in terms of manufacturing time, cost, resources utilisation, bottlenecks, and throughput. Section 2 & 3 of this paper provides a brief overview of various modelling approaches and their relevance to biopharmaceutical process modelling along with the challenges in their adoption in GT industries. Section 3 outlines the methodology employed to develop a DES model to support 'what-if' scenario planning along with a case study from a biopharmaceutical company (Section 4).

2. Approaches in Biopharmaceutical process and business modelling

Decision-making in drug development is increasingly relying on tools that capture dynamic process data and facilitate representation of technical/business aspects of drug development. Fig. 1 illustrates the application of such tools in various stages of biopharmaceutical drug development as depicted by Ashouri (2001) [7]. Despite the range of application, their utilisation is not as seamless in process industries as it is in mature manufacturing industries such as Automobile/Aerospace. This may be because the GT industries are still developing their core technology and the use of computer-aided tools in process planning and optimising is a novelty [8]. Furthermore, Saraph (2001) [9] regards biopharmaceutical as complex manufacturing characterised by:

- Lack of well-defined processes with a mix of discrete and continuous flows
- Intermediate quality control and assurance processes between production stages
- Non-uniform batch sizes and buffer sizes that vary significantly from stage to stage
- Highly uncertain production output due to shorter shelf-life of products and higher rejection rates
- Limited standardisation/automation with manual handling of materials
- Stringent regulations, adherence to Good Manufacturing Practices (GMPs) creating further operational constraints

2.1. State of the art methodologies and tools

Despite the challenges, many researches have considered computer-aided process design, simulation, and scheduling tools to enhance the understanding of bioprocesses and to develop test cases for evaluation [10, 11]. Usage of these computer-aided tools in the biopharmaceutical industry falls broadly into four categories as depicted in Fig. 2. Although this classification distinguishes one methodology from another, in practice, most of the tools developed for industries are a combination of one or more of these methods.

Mathematical programming is the oldest and traditional method involves building mathematical relationships between variables to technically represent the unit operations. For example, mass balance equations created using spreadsheets or general-purpose simulators such as SPEEDUP by Aspen Technology (12), Matlab (13), and Labview by National Instruments (14) are used to model unit operations in biopharmaceutical manufacturing. These methodologies do not have the capability to visualise unit operations in real time. Therefore, mathematical modelling methods have slowly evolved to use graphical user interfaces. Hierarchical modelling approaches developed by Farid et al [15] uses Object Oriented Programming (OOP) implemented in a graphical simulation tool (ReThink) to simulate the key activities in manufacturing such as resource utilisation and cost. This method combines both process modelling using mass balance methods for plant design and capacity management, and business modelling using techniques such as investment appraisal, risk evaluation, and production planning.

Karri et al [16] has also applied the OOP methodology to model not just the key tasks but also other activities in the manufacturing stage. Furthermore, in another study, Lim et al. [17] extends this hierarchical approach to include additional tasks such as QA/QC and documentation using a DES based tool (ExtendSim). Whilst, mathematical programming and DES methods are deterministic, Rajapakse et al. [18] has developed a tool to model the uncertainties in biopharmaceutical product portfolio management to predict the outcome of various development strategies using techniques such as Monte Carlo Simulation and Sensitivity Analysis. It quantifies the outputs in the form of economic metrics such as Net Present Value (NPV) to support decision-making. Application of stand-alone DES packages also allow stochastic and dynamic modelling of biopharmaceutical processes/systems aimed for capacity planning, scheduling, debottlenecking, and water minimisation [8, 9]. Another tool developed by Sharda and Bury [19] has shown the potential application of DES model (built in ExtendSim) in the maintenance stage. On the other hand, optimisation methodologies employed by Petries [20] uses SuperPro Designer simulation package to account for batch process simulation rather than unit operation simulation.

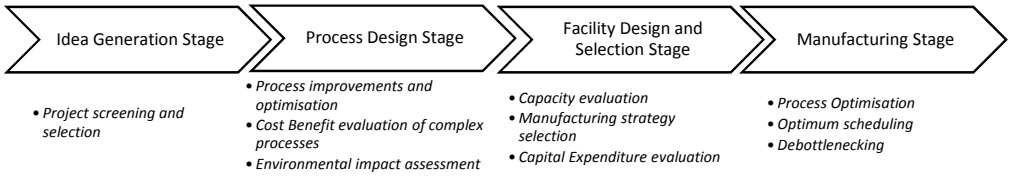

Fig. 1. Computer-aided tools in biopharmaceutical product development (adapted from Ashouri (2001) [7])