APPLICATION OF QUALITY BY DESIGN CONCEPTS AND AUTOMATION TO IMPROVE MANUFACTURING PROCESS CONSISTENCY OF DEVELOPMENT AND CLINICAL-STAGE CELL THERAPIES

Peter Mitchell, Centre for Biological Engineering, Loughborough University
P.D.Mitchell@lboro.ac.uk
Kieran O'Donovan, ReNeuron
Mark McCall, Centre for Biological Engineering, Loughborough University
Robert Thomas, Centre for Biological Engineering, Loughborough University

Key Words: Cell therapy, Manufacture, Automation, Quality by Design

Designing manufacturing processes to reproducibly generate process-sensitive human cells of sufficient quantity and quality for clinical application is challenging and complex. Manufacture of cell therapies in manual flask based processes is controlled primarily through adherence to detailed SOPs which may contain subjective user interventions and relatively poorly defined operating controls. This situation can lead to clinical production processes with limited control of critical quality attributes, significant reliance on endpoint quality testing and consequent product wastage. Applying systematic and data driven approaches to process development, many of which form part of the Quality by Design (QbD) toolset, reduces manufacturing process risk. We have applied these approaches with a series of partners and cell types to demonstrate application of QbD tools to cell therapies. This includes statistical capability analysis to define process confidence limits for expansion processes, to identify sources of process variability, and to quantify process performance in relation to the process specification and necessary scale. This further enables risk assessment and gap analysis to identify and prioritise key manufacture process risks with common recurrent elements including input materials, cryo-strategy, and operational parameters pertaining to culture and medium supply strategy. Key variable screening via statistically designed experiments has enabled improvement in process consistency across multiple operations and an improved understanding of process tolerance to parameter levels. It also highlights where automation could be applied to enhance process reproducibility and increase process scale whilst retaining process format with comparability to prior manufacturing development. CompacT SelecT automated manufacturing processes have demonstrated consistently greater cell yields than manual processes with statistical analysis showing significantly improved confidence intervals between multiple production batches and facilitating identification of remaining sources of variation for further targeted process improvement. Example case studies include a partnership with ReNeuron, a UK-based stem cell therapy business currently undergoing a phase II clinical trial with its CTX cell therapy candidate to enhance motor recovery in disabled stroke patients, to develop scalable robust production processes for the CTX cell line.