Manufacturability and ITS impact upon cell-based product process design [Abstract]

MANUFACTURABILITY AND ITS IMPACT UPON CELL-BASED PRODUCT PROCESS DESIGN

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Manufacturing process design for cell-based therapies (CBTs) poses special challenges arising from their complexity and sensitivity. Their fundamental behaviour differs from medicines based on synthetic or biological molecules. Small numbers of cellular impurities may have a disproportionate influence over batch quality. A high level of predictability of quality is necessary to meet this need. A product that satisfies this need may be termed 'manufacturable'. Current regulations are based on the conventional drug paradigm and this is not helpful in meeting quality assurance targets for CBTs.

In this paper the factors that contribute to 'manufacturability' are reviewed with special attention to research in two additional fields.

For a process to be formally 'capable' it must have a failure rate that is acceptably low. 'Six-sigma processes' are defined using Gaussian distributions. CBTs and their starting materials exhibit distinctly non-Gaussian behaviour. Outlier events can have a strong influence on batch safety and efficacy.

Process design is subject to a further challenge that arises from the difficulty in ascertaining the variability in each measurement itself. Flow cytometry results vary from one instrument to another making it difficult to quantify the variability in measurement and thus to define measurement uncertainty as a whole. In more traditional mechanical and chemical engineering studies this deficiency is less threatening to process design.

We propose that two tools require more focused research to allow them to be used more widely.

Parametric release requires detailed quantitative understanding of the relationship between conditions of manufacture and product attributes. Autoclave sterilisation is based upon a six-log reduction in bioburden using this approach. A process validation study for CBTs may similarly establish control conditions within which cellular impurities occur with a level of probability sufficient for them to be assumed absent even when the number is below the limit of detection for a single batch.

Emphasis to date has been on control strategies using stochastic principles. Interdependent behaviour of cells requires modelling based upon work at small scale. Such models will need to be verified using the boundaries of the control state on the plant floor.

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