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Process analytical technologies and real time process control a review of some spectroscopic issues and challenges

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ABSTRACT

Process analytical technologies (PAT) are increasingly being explored and adopted by pharmaceutical and industrial biotechnology companies for enhanced process understanding, Quality by Design (QbD) and Real Time Release (RTR). To achieve these aspirations there is a critical need to extract the most information, and hence understanding, from complex and often 'messy' spectroscopic data. This contribution reviews a number of new approaches that have been shown to overcome the limitations of existing calibration/modelling methodologies and describes a practical system which would enhance robustness of the closed loop process control system and overall 'control strategy'. Application studies are described of the use of on-line spectroscopy for the monitoring and control of a downstream solvent recovery column, batch cooling crystallization and pharmaceutical fermentation.

1. Introduction

In 2004 the FDA published its process analytical technology (PAT) guidance [1] and the cGMPs for the 21st Century [1] which calls for the design of effective and efficient manufacturing processes to assure product quality and performance; product specifications based on a mechanistic understanding of how different formulations and processes affect product performance and continuous real time assurance of quality. Following on in 2005, the European Medicines Agency (EMEA) published its Road Map to 2010 'Preparing the Ground for the Future'. These publications released the potential for significant changes in the development and manufacturing of pharmaceuticals.

Folestad [2] has described *PAT* as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." *QbD* as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management" (definition in ICH Q8R, Annex to ICH Q8: Pharmaceutical Development). This is not entirely new since the industry has always used *QbD* to some extent to design and build quality into product and manufacturing process quality, rather than 'testing-for-quality', for example the contributions of Deming and Shewart (Edwards Deming, http://asq.org/about-asq/who-we-are/bio_deming.html and Walter Stewart http://asq.org/about-asq/who-we-are/bio_shewhart.html); which in essence forms a corner stone of the PAT/QbD in monitoring and improving product and processes understanding, reducing variability and using quality risk management to focus resources into areas critical to the patient. This approach aligns with continual process improvement (e.g. lean six sigma); and enhanced innovation by reducing regulatory burden associated with changes. *Design Space:* as "The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality" where working within the design space is not considered as a change (definition in ICH Q8: Pharmaceutical Development), and *Quality:* as "The suitability of either a drug substance or drug product for its intended use, including such attributes as the identity, strength, and purity"; with one of the ultimate aims of the FDA PAT being that of *Real Time Release:* defined as "A system which ensures that a product is of the intended quality, while reducing or (in some cases) making end-product testing redundant, by utilising an appropriate combination

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