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RESEARCH ARTICLE

PAT within the QbD Framework: Real-Time End Point Detection for Powder Blends in a Compliant Environment

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Abstract
Introduction A process analytical technology (PAT) method using a near infrared (NIR) spectrometer attached to a drum blender was developed for real-time end-point detection for an extragranular blend.
Methods and theory The method and corresponding documentation are part of the control strategy for a recently filed and approved pharmaceutical product, and the method is currently in place and in use for manufacturing of this pharmaceutical product at GlaxoSmithKline.
Results and discussion The immediate benefits are a dramatic reduction in blend time as well as real-time verification of blend homogeneity for every batch. The development of the blending end-point method is presented and a set of fundamental requirements for developing any PAT method is proposed.
Conclusion It is discussed how the reported PAT end-point method fits with the proposed PAT framework, and the validation aspects required to achieve a compliant method for use in drug product manufacturing are presented.

Keywords QbD · PAT · Blend · Chemometrics · NIR · Compliant

Introduction

In a quality by design (QbD) environment, the objective is to build quality into the product through the development process, and process and product understanding are essential in order to achieve this goal. The process and product understanding provided by a successful development process can be used to devise a control strategy to ensure the manufacture of consistent right quality products.

One of the possible elements in a control strategy is process analytical technology (PAT) [1]. PAT can be defined as a mechanism to design, analyse, and control pharmaceutical manufacturing processes through the measurement of critical process parameters (CPPs) which influence critical quality attributes (CQA). PAT can also be used to measure CQAs directly and thus enable real-time release testing. Usually, the PAT concept is implemented using a relevant sensor for in-process measurements and a model translating the measured signal into the property of interest, e.g., assay or in-specification/out-of-specification. To facilitate the implementation of a PAT method, there are further requirements with respect to software, data transfer/automation, and business processes for operating the method as well as acting on the method output.

Generally there are five fundamental requirements to PAT methods intended for use in regulated environments:

1. Basic understanding of process
   Before starting the development of a PAT method, there must be some knowledge about what a good process looks like, i.e., what are the CQAs, and preferably some understanding about what the CPPs are, i.e., how to achieve satisfactorily CQAs. A complete understanding of the process is however not required as PAT can be used to refine or expand the process understanding.
2. Ability to measure
   After identifying what is important in the process, it is necessary to ensure that the considered measurement

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