Title: Use of Process Analytical Technology in Process Validation					
Guidance Number: 97					
Prepared by:		Date:		Supersedes:	
Checked by:		Date:		Date Issued:	
Approved by:		Date:		Review Date:	

Introduction

This document provides examples of the possible use of Process Analytical Technology (PAT) systems during traditional process validation to demonstrate that a manufacturing process is in a validated state. This guidance is supplemental to guidance ôProcess Validation for Drug Products and Medical Devicesô and ôProcess Validation for Active Pharmaceutical Ingredients (API)ô.

PAT systems can be used to:

- Collect data in parallel with the collection of traditional process validation data
- Reduce the traditional validation testing or
- Replace a traditional test (regulatory or an in-process release test) during process validation.

Whatever type of use, PAT testing can provide an opportunity to increase data analysis and process knowledge compared to traditional tests. This guidance includes examples of PAT applications for each of the three scenarios listed above. Modification of registration documentation to support the replacement of a registered method by a PAT application must comply with local and international regulatory requirements.

Recommendations and Rationale

PAT system application in process validation offers the opportunity to leverage experience with scientific inquiry and innovation. If possible, it is recommended to utilize PAT to evaluate a process before validation begins. This will establish a baseline for comparisons in later studies and provide an opportunity to evaluate the PAT approach itself.

This guidance provides an example of approaches for applying PAT in support of process validation activities. PAT may be applied in three primary forms;

1. Parallel PAT activity - traditional validation occurs without change while PAT activity is added and performed concurrently to traditional validation. The PAT provides additional information about the process, quality attributes and/or parameters. If the traditional process validation criteria are met but the PAT data suggest that the process might need further evaluation, an investigation should be initiated. If the PAT results are related to product quality, lot release should be held until the PAT investigation is completed.

2. QC reductive PAT activity ï the PAT activity is integrated into the validation approach to provide information that will assist in the conclusion of the validation exercise. Alternatively, the PAT activity could be applied to reduce the volume or frequency of traditional validation testing. Integration into traditional validation documentation and potential alteration to traditional validation testing can mean that the PAT testing may come under regulatory scrutiny.

3. Alternate PAT activity ï the PAT activity is integrated into the validation approach and traditional testing is replaced by alternate PAT methods. PAT data directly affects the outcome of the validation exercise and would come under regulatory scrutiny.

Appendix I

Example 1: Near Infrared (NIR) Analysis of Active Ingredient during process validation of blending operations

Components of a drug product mixture are blended in a rotating blender to achieve a homogenous mixture for compression into tablets. The validation activity is to demonstrate equivalence of active content distribution following a process change. The PAT system is NIR for blend analysis. It is well established and could take the form of in-line monitoring of the blend within the blender (e.g. using Corona or ePAT601 system) or at-line/off-line monitoring of samples taken from the blender (e.g. using Bruker Multipurpose Analyzer).

NIR analysis of the active content can be applied in each of the three PAT support approaches. The choice of approach of PAT support will depend on the product and the individual validation activity. An example of how NIR analysis could be applied for each approach is discussed below.

Parallel PAT Activity:
The Parallel PAT approach was applied to an evaluation of a process during a product transfer. This approach was chosen because the PAT application had not been applied to the product previously, final blend testing is registered (no scope for reducing QC testing), and there was insufficient time to validate the PAT method as an alternate analytical method.
A separate PAT protocol was prepared that detailed:

- a feasibility study would be performed to establish an appropriate qualitative method for analysis
- the frequency of on-line NIR applied throughout the blending to monitor the blending profile
- final blend samples would be sampled by thief for at-line NIR analysis
- statistical comparisons would be performed to establish equivalence of validation batches to each other (at 95% confidence level)

The protocol was executed, PAT testing performed and the results reported in a PAT Report.

An example of blending profiles achieved during process validation is shown below. The blending profile for Batch 1 exhibits potential de-mixing. Batch 1 was later found to have poor dissolution properties. The PAT measurement has provided additional insight into understanding where in the process there is an impact of a process variation on this product.

Appendix II

Example 2: Near Infrared (NIR) Analysis of Active Ingredient during process validation of tabletting operations

A drug product blend is compressed into tablets of uniform unit dose. The validation activity is to demonstrate equivalence of active content throughout the tabletting process following a process change. The PAT system is NIR for tablet analysis. It is well established and could take the form of in-line monitoring of the compressed tablets (e.g. using Bruker Tandem 2) or at-line/off-line monitoring of samples taken from the tablet press (e.g. using Bruker MPA).
NIR analysis of the active content can be applied in each of the three PAT support approaches. The choice of approach will depend on the product and the individual validation activity. An example of the how NIR analysis could be applied for each approach is discussed below.

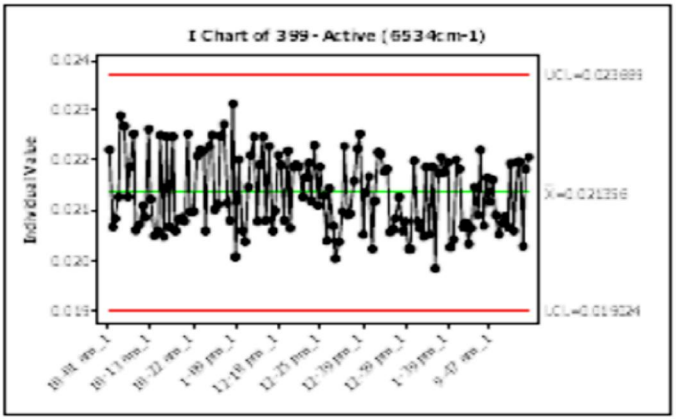
Parallel PAT Activity:
The Parallel PAT approach was applied to a product during introduction onto a new tablet press. This approach was chosen as the PAT application had not been applied to the product previously, and traditional validation protocols had already been established. The NIR method was not yet validated as an alternate analytical method.

Separate PAT documentation was prepared that detailed:

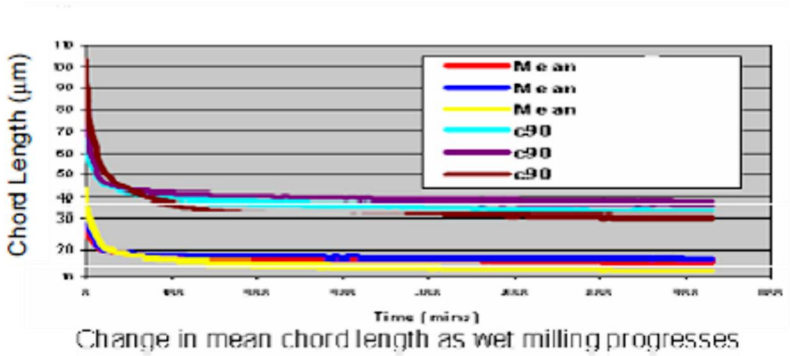
- a feasibility study would be performed to establish an appropriate qualitative method for analysis
- the frequency of sampling for NIR throughout the tabletting
  - at least 7 tablets taken at the 20 locations to be used for the PQRI[8] content uniformity testing
  - 60 tablets taken from start, middle and end of the process
- statistical comparisons to be performed to establish equivalence between the validation batches to each other (at 95% confidence level).

The protocol was executed, NIR testing performed and the results reported in a PAT Report. All traditional QC validation testing continued unchanged according to the separate validation documentation, including samples (3 tablets at 20 locations) and batch end of run release testing (10 random tablets from throughout the process).
An example of the graphical output from the statistical evaluation of tabletting data from one batch is shown below. Frequent sample analysis from throughout the process (7 tablets at 20 locations) and statistical process control charts allows for identification of trends and tablets exhibiting outlier behaviour.

The batch shown shows a mild trend of reducing absorbance (seen in Xbar R chart), all tablets are within the control limits and no tablet has been identified with outlier characteristics.

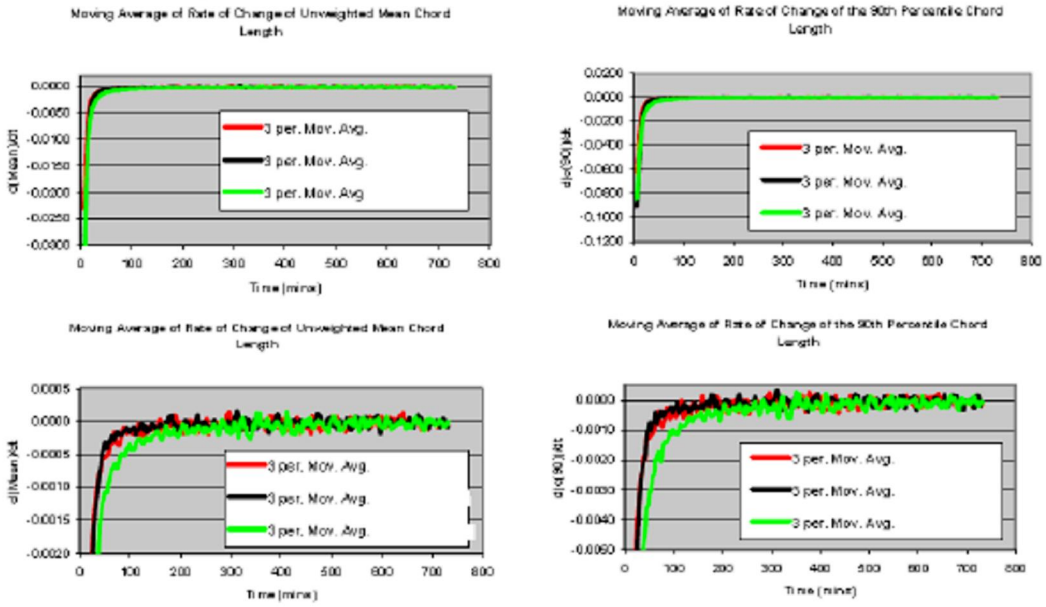


Appendix III (Cont.)



Change in mean chord length as wet milling progresses

The rate of change plots (zoomed in the lower plots) clearly demonstrate the wet milling process has reached an endpoint in under 30minutes.



Appendix III (Cont.)

QC reductive PAT Activity:

An opportunity exists for the above example PAT activity where the QC reductive PAT approach could be applied.

- The FBRM method could be used to verify at real time when the wet milling process is complete
- The FBRM method could be used to reduce the number of QC samples taken to verify wet milling completion

Alternate PAT Activity

An opportunity exists for the above example PAT activity where the Alternate PAT approach could be applied.

- The FBRM method could be used as the primary mechanism to control particle size. With a regulatory submission and appropriate method validation, FBRM based control of the final particle size could be used to replace the finished product particle size testing.

