Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
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 'Process Validation for Drug Products and Medical Devices' and 'Process Validation for Active Pharmaceutical Ingredients (API)'.

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.

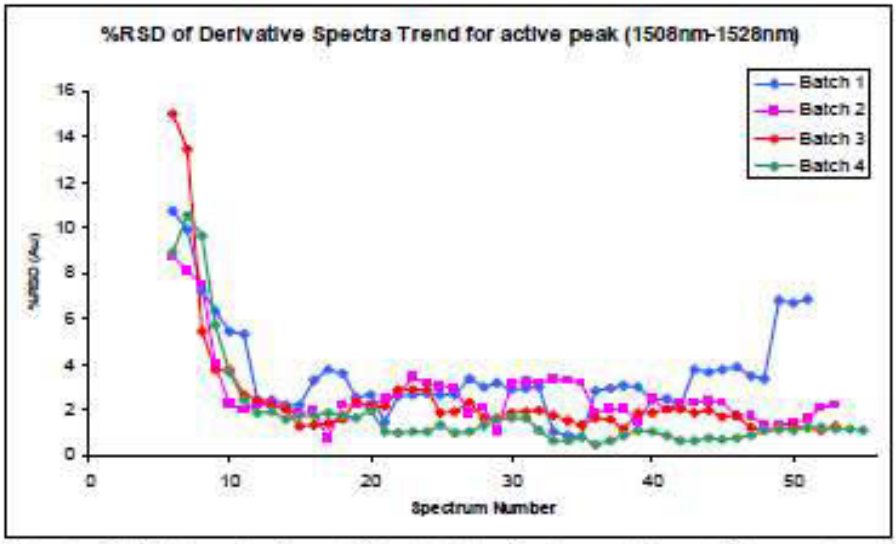
PAT system application in process validation offers the opportunity to leverage experience with scientific inquiry and innovation. If possible, it is recommended to utilize PAT to evaluate a process before validation begins. This will establish a baseline for comparisons in later studies and provide 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 – 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 – 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.
Some reasons for selecting the different approaches are as follows:
- Limited past experience of applying the PAT for a particular product may suggest initial Parallel Approach



An example of the statistical evaluation of blend data is shown below. The greater variability and shift in active absorbance in Batch 1 can be clearly seen in the individual plot. An analysis of variance (ANOVA) demonstrated that the variation in Batch 1 was statistically significantly different to the other batches. A further ANOVA between the remaining 3 batches (shown below) demonstrated that there was no significant difference in variability in the 3 batches and that the 95% confidence interval of the means overlapped. Batches 2 through to 4 where therefore shown to be equivalent to one another.

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.

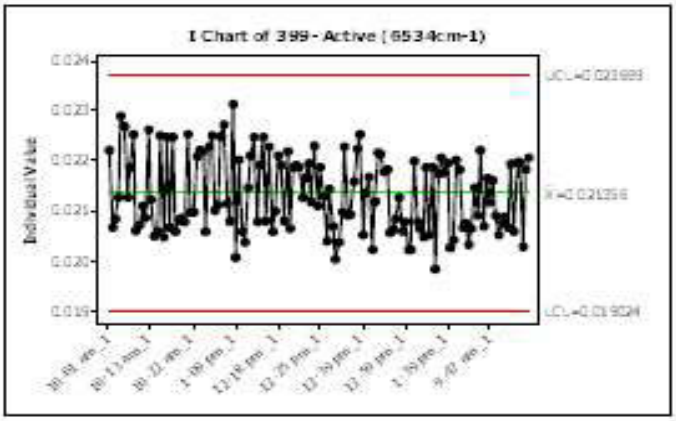
Parallel PAT Activity:
The Parallel PAT approach was applied to a product during introduction onto a new tablet press. This approach was chosen as the PAT application had not been applied to the product previously, and traditional validation protocols had already been established. The NIR method was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

Example 4: Mid Infrared (MIR) Analysis of Active Pharmaceutical Ingredient(API) reaction endpoint

An intermediate reaction step involves controlled addition of a key reactant to drive the reaction to completion. The validation activity will demonstrate that the reaction had gone to completion and that levels of impurity formation were minimized.
The PAT system is a Mid Infrared analysis used to monitor the reaction at real time. MIR data are used to demonstrate that the reaction has reached completion

MIR analysis of the reaction 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 the how MIR analysis could be applied for each approach is discussed below.

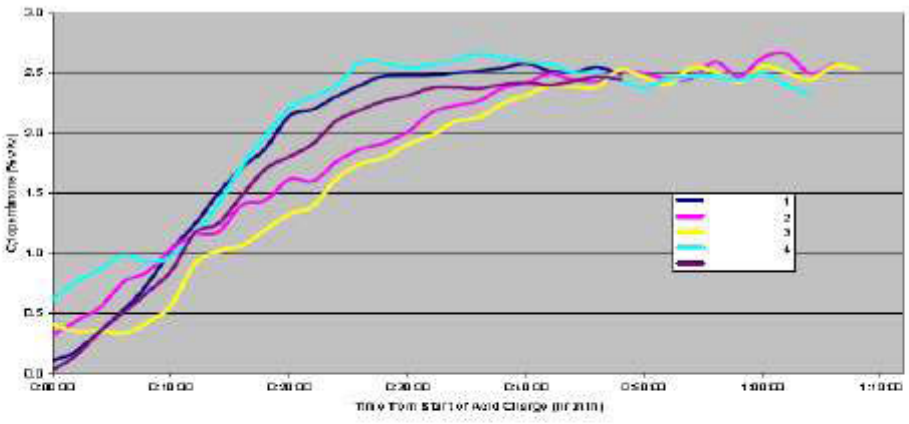
Parallel PAT Activity
The Parallel PAT approach was applied to monitor the reaction. This approach was chosen as this was the first plant scale demonstration of the technology.
In this instance all PAT data were captured in a final PAT Report. In a formal validation run a separate PAT protocol would be prepared to detail the following:

- How MIR would be applied throughout the reaction process
- Statistical comparisons to be performed to establish equivalence of validation batches to each other (at 95% confidence level) and with lots previously produced (pre-change)

Note: Equivalency and homogeneity demonstration studies are still a requirement for Process Validation. For more information on these topics for API refer to GPB-T4046 and GPB-T4047. For Drug product refer to GPB-T4074.

- Sampling plan required to demonstrate that the MIR indicated endpoint was valid

The plot below illustrates how MIR was used to demonstrate that the process had reached a stable plateau endpoint.



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

- The MIR data could be used to determine when to take validation samples for off line analysis

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

- The MIR data could be used to replace the off-line testing of samples, with the MIR data indicating when the reaction was complete.

