Guidance Number: 097

Figure:

	Parallel PAT	QC Reductive PAT	Alternate PAT
Process Validation Documentation	Separate protocol and report to traditional validation protocol	Incorporated into traditional validation documentation	Incorporated into traditional validation documentation
PAT Method Type	May be quantitative or qualitative	May be quantitative or qualitative	Typically quantitative
PAT Method Documentation	"Fit for purpose"* validation may be documented separately or within PAT protocol/ report	"Fit for purpose" validation should be documented separately	Separate validation documentation to document method as alternate to registered test methods
Sampling Plan	No impact on traditional sampling plan	Traditional sampling plan may be altered	Traditional sampling plan may be altered or replaced
Validation Testing	No effect on traditional validation testing	PAT may be used to reduce quantity of QC validation testing or target QC validation testing	Traditional testing may be replaced in part or full by PAT
Batch Release Testing	Performed by traditional QC testing	Performed by traditional QC testing	Performed by traditional QC testing or PAT method (with appropriate method registration)
Data style	PAT results provide information only and may not have set acceptance criteria	PAT results have associated acceptance criteria	PAT results have associated acceptance criteria

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).

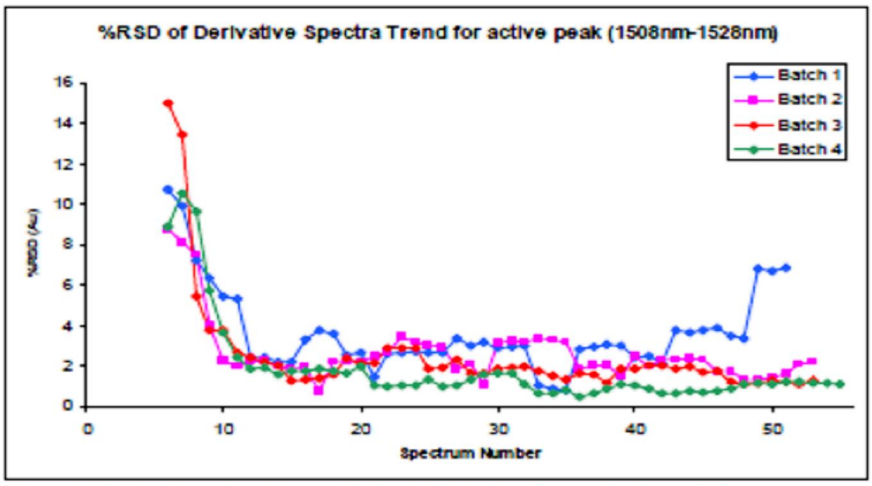
NIR analysis of the active content can be applied in each of the three PAT support approaches. The choice of approach of PAT support will depend on the product and the individual validation activity. An example of how NIR analysis could be applied for each approach is discussed below.

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:

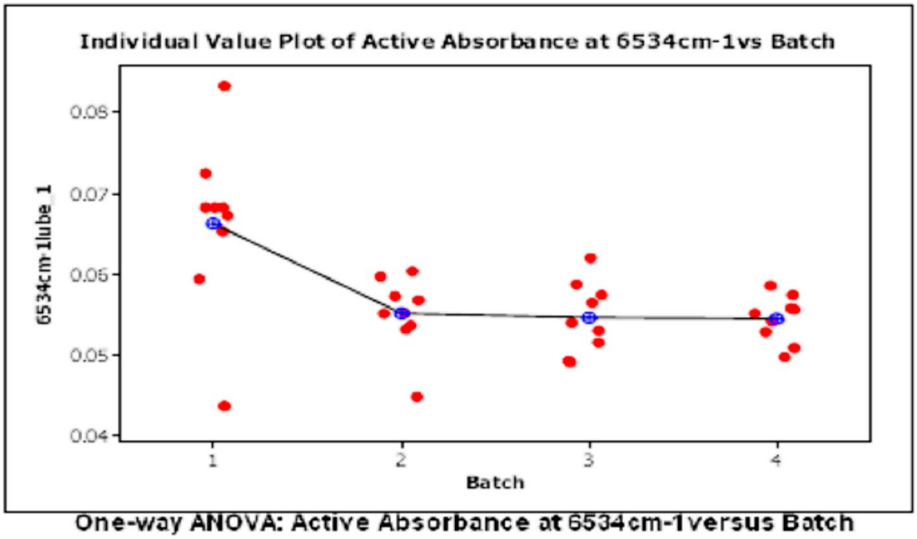
- a feasibility study would be performed to establish an appropriate qualitative method for analysis
- the frequency of on-line NIR applied throughout the blending to monitor the blending profile
- final blend samples would be sampled by thief for at-line NIR analysis
- statistical comparisons would 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.



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.



One-way ANOVA: Active Absorbance at 6534cm-1versus Batch

```
Source  DF         SS          MS      F      P
C21      2  0.0000020   0.0000010   0.06  0.941
Error   24  0.0003932   0.0000164
Total   26  0.0003952
S = 0.004048   R-Sq = 0.50%   R-Sq(adj) = 0.00%

                                Individual 95% CIs For Mean Based on
                                Pooled StDev
Batch  N      Mean     StDev   -------+---------+---------+---------+--
2      9  0.055079  0.004606       (----------------*-----------------|
3      9  0.054583  0.004428    (----------------*-----------------)
4      9  0.054447  0.002885   (----------------*-----------------|
                                -------+---------+---------+---------+--
                                     0.0528    0.0544    0.0560    0.0576

Pooled StDev = 0.004048
```

QC Reductive PAT Activity:

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

- If blend testing was not a regulatory requirement, traditional QC blend testing could be reduced. For example, a reduced number of samples could be QC tested while each sample is

tested by NIR or where composites are used for QC testing to demonstrate active assay, while NIR is used to demonstrate active distribution.

Alternate PAT Activity:
Possible opportunities exist for the above example PAT activity where the Alternate PAT approach could be applied.

- If blend testing is not a regulatory requirement, QC testing could be removed altogether with the NIR results demonstrating the completion of the blending process and content uniformity could be demonstrated by more extensive testing at tabletting stage.
- If a validated PAT method was already available for the product, the alternate PAT approach could be used and the QC traditional testing removed without regulatory impact (i.e. regardless of whether blend testing is a regulatory requirement).

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.

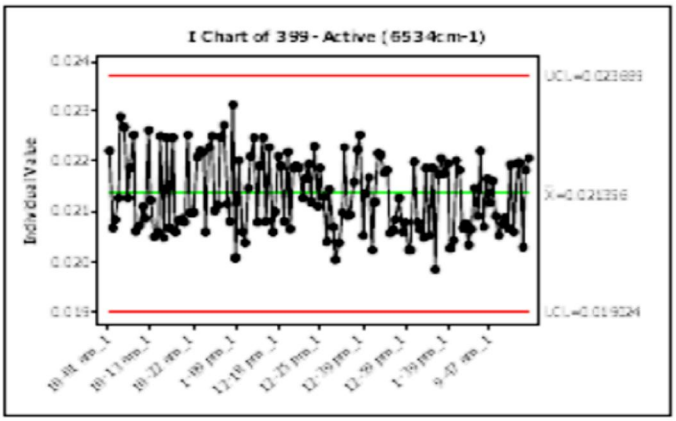
Parallel PAT Activity:
The Parallel PAT approach was applied to a product during introduction onto a new tablet press. This approach was chosen as the PAT application had not been applied to the product previously, and traditional validation protocols had already been established. The NIR method was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

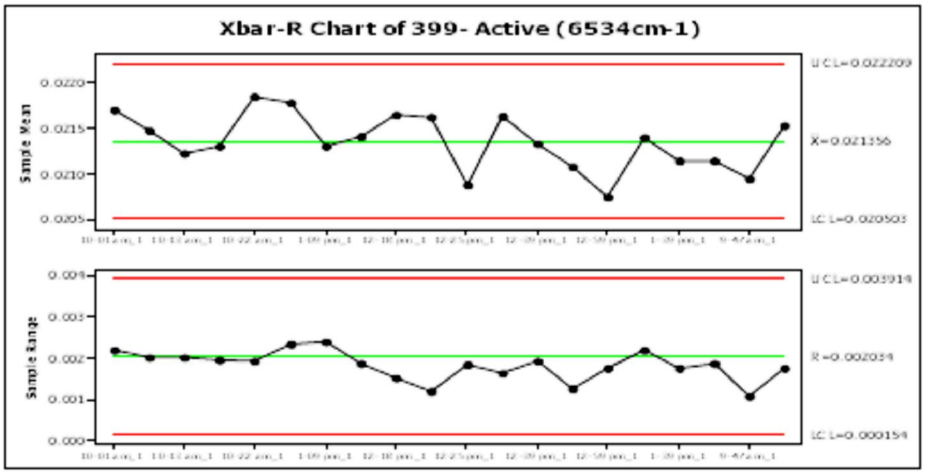
Separate PAT documentation was prepared that detailed:

- 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).

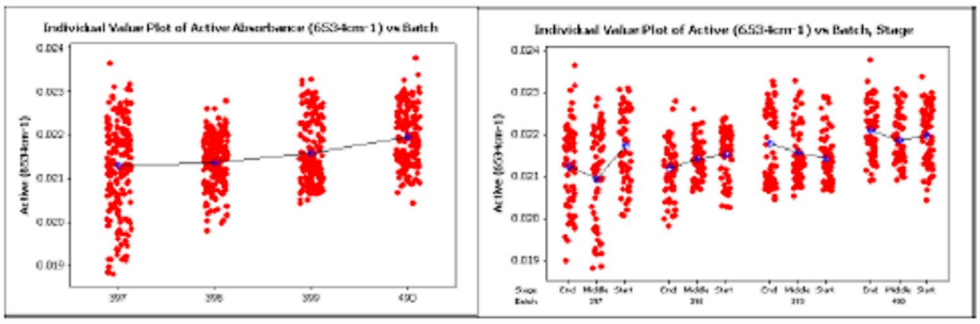
The protocol was executed, NIR testing performed and the results reported in a PAT Report. All traditional QC validation testing continued unchanged according to the separate validation documentation, including samples (3 tablets at 20 locations) and batch end of run release testing (10 random tablets 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.





Batch to Batch comparisons were performed based on large volumes of tablets. The plot below left shows all tablets analyzed from the 20 locations while the plot on the right shows the 60 tablets from start middle and end of the tabletting process. ANOVA analysis demonstrated that the increased variation seen in Batch 1 was found to be statistically significant. Despite this significant difference, all results showed the tablets from batch 1were acceptable in quality.



QC Reductive PAT Activity:

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

- Since the PQRI testing is not a regulatory requirement but a guideline, the NIR analysis could be used to demonstrate the normality and spread of the active content of the tablets. The NIR analysis could then be used to target the QC laboratory assay on a reduced number of tablets that cover the absorbance range, or at the extremes of the absorbance range to fully characterize the active content distribution. This has potential to reduce the laboratory validation testing from 60 to a greatly reduced number (e.g. 10). Batch release testing would remain by the traditional method.

Alternate PAT Activity:

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

- If a validated PAT method was already available for the product the alternate PAT approach could be used to remove the QC traditional testing without regulatory impact. Batch release testing could remain by the traditional method.

Appendix III

Example 3: FBRM (Focus Beam Reflectance Measurements) analysis of Particle Size during process validation of wet milling operation

An API suspension is recycled through a high shear mill to achieve a uniform and acceptable particle size. This step is used in place of dry milling to ensure product containment. The validation activity is to demonstrate during the start up of a new process that the mill is capable of producing material of consistent particle size from lot to lot and that the particle size distribution reaches a stable endpoint after the prescribed duration or number of passes through the mill. The PAT system is a FBRM for particle size analysis. It is well established and takes the form of an in-line analyzer measuring the API particles in suspension in a pipe on the mill recycle loop. At-line/off-line monitoring of samples taken from the mill is performed using off-line laser diffraction analysis.

FBRM particle size analysis of the mill output 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 FBRM analysis could be applied for each approach is discussed below.

Parallel PAT Activity:

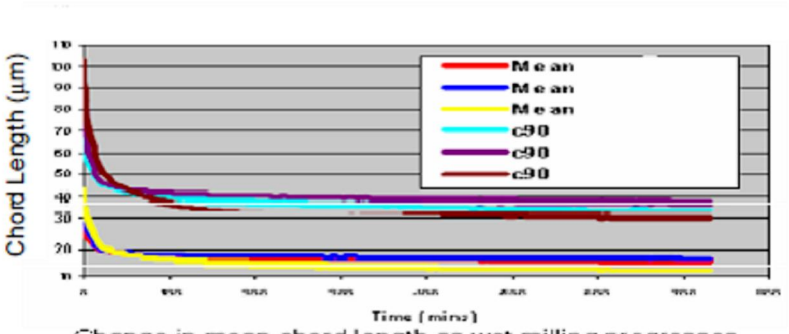
The Parallel PAT approach was applied to the API validation lots. This approach was chosen as it was felt that it was the lowest risk approach and would not impact regulatory submission timelines.

Separate PAT documentation was prepared that detailed:

- How FBRM would be applied throughout the wet milling operation
- Process end mill samples to be sampled for off-line laser diffraction analysis (done to verify results using the traditional analytical method)
- statistical comparisons to be performed to establish equivalence of validation batches to each other (at 95% confidence level)
- Sampling plan required to demonstrate that the FBRM indicated endpoint was valid

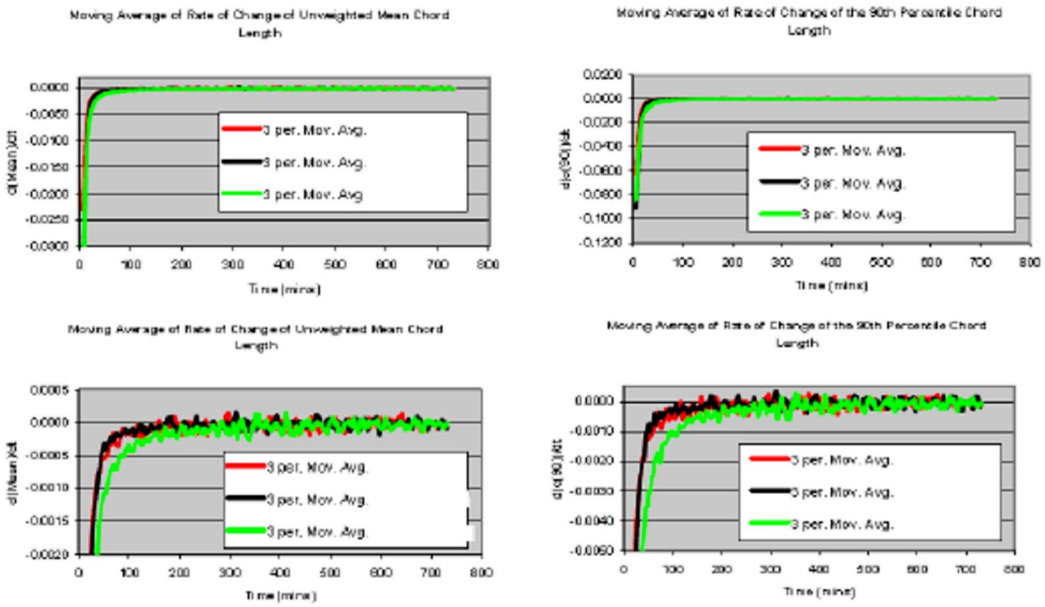
The results were reported in a PAT Report. The plots below show how the FBRM data were used to demonstrate that wet milling endpoint was achieved for each of 3 lots. The plot below shows the profile of the milling process, showing the change in mean chord length(calculated length obtained from the reflected laser light as it passes across the particle surface) and c90 values (Chord length for 90% of particles passing the FBRM).

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.)

<u>QC reductive PAT Activity</u>:

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

<u>Alternate PAT Activity</u>

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.

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.

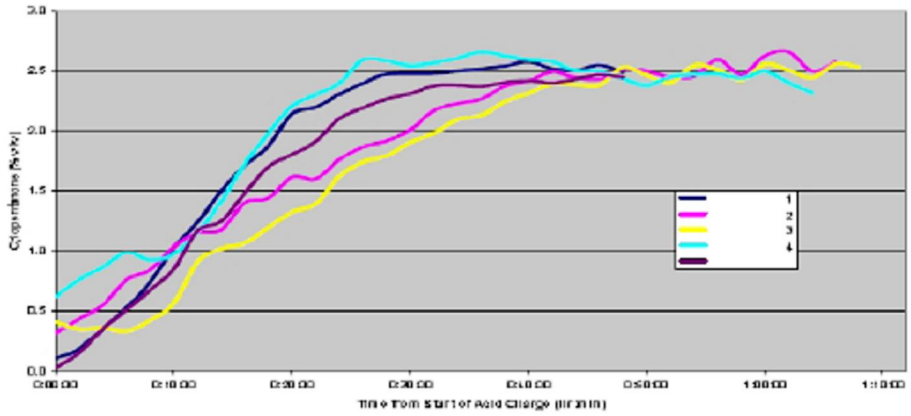
Parallel PAT Activity
The Parallel PAT approach was applied to monitor the reaction. This approach was chosen as this was the first plant scale demonstration of the technology.
In this instance all PAT data were captured in a final PAT Report. In a formal validation run a separate PAT protocol would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