

PAT R&D efforts in pilot plant (proof of concept and suitability for application in manufacturing)

What should be documented to justify suitability?

- R&D explores boundaries of processes for “understanding”. R&D focus is different. Use PATs for “process understanding”, versus PATs for “process control” in manufacturing. Provides opportunity for “process control”.
- Not all PATs will make it to manufacturing. Identify the PATs that should be used in manufacturing.
- Demonstrate suitability of PAT measurement for intended use. e.g. For predicting end product quality attributes.
- Demonstrate it is validatable, e.g. Sensor suitability, location of sensors, number of sensors, as well as traditional measurement attributes.
- PAT performance requirements are more rigorous if the intended use of PATs, either individually or combined, is to replace end product testing.

PAT R&D efforts in manufacturing:

What should constitute acceptable verification of suitability and validation?

- Points stated above in R&D section will apply with the following additions:
- Transferability of PAT should be investigated. Equipment design, scale up issues, interface change, ongoing calibration, maintenance, equipment qualification, safety (e.g. operator, potential contamination of product).
- Refinement of models will be needed, e.g. “process signature” developed in R&D, based on limited information.
- Concept of PAT can be submitted as a “protocol” in an original NDA, or as a prior approval supplement. Implementation of PAT can be done through a less burdensome filing mechanism, e.g. CBE supplement, or Annual Report.

Routine manufacturing using PATs:

What should be the regulatory standard for accepting an on-line measurement to replace end product testing?

Level of built-in redundancy?

- Body of PAT information should have equivalent or better informing power than the corresponding conventional approved end product tests.
- Recommend setting-up a table, showing relationship between PAT testing and current testing methodology.
- Parallel PAT testing and conventional testing (in-process and/or release tests) should be performed for a sufficient number of batches (a minimum of three batches in the absence of historical manufacturing data).
- Level of redundancy is often a business decision.

Identify steps for resolving OOS observations:

Under what conditions can end product testing be used to resolve OOS observations?

- PATs may allow selective rejection, or partial batch release.
- Within batch trend information available with PATs facilitates resolution of OOS observations.
- Until PAT test results are approved for regulatory purposes, the approved conventional test results supersede the PAT results.
- If the OOS result is traced to instrument failure, then traditional approved analytical methods can be utilized for batch release in lieu of PAT based result.

Using on-line NIR (for blend, dry, content, dissolution) and HPLC as examples of PAT, please outline the essential experiments (hypothesis or questions) that should be conducted by a company to successfully develop and validate these tools for use in manufacturing operations.

What criteria should be used to ensure that relevant critical formulation/process variables have been identified and appropriate PAT tools selected to ensure their optimal control?

Criteria should be based on

- Product performance
- Adequate Process Control
- Assurance of Product Quality

PATs either individually or in aggregate are predictive of final product quality.

What information should be collected to justify use of indirect measurements (e.g. signature or correlations) that relate to product quality/performance attributes?

- Process and Product signatures are a sum of multiple measurements.
- Demonstrate link between PAT parameter and product characteristics.
- Surrogate should be scientifically based.
- Acceptable variability in population should be established.

When and to what extent would FDA involvement facilitate PAT R&D and application projects?

- Issue guidance. Define terms, provide a glossary.
- Develop training programs; both internal and external.
- Develop workshops; and include case studies, mock submissions.
- Provide meetings between Agency and Applicants.
- Global harmonization, ICH guidance.