Guidance Number 028:

Table 1. Risk assessment of Potential CPPs and controls for drying operation

Process control	Acceptable range	Why chosen
Air flow	100-150 ft^3/min; target point is 125 ft^3/min.	Important for consistent drying results. Acceptable range shown for pilot scale, probably greater for production scale. Lower flow rates do not suspend particles for drying; higher flow rates can dry product too rapidly and send excessive amount of product into filter socks. Flow rate easily controlled to prevent out of range flow rates. Not critical to product quality.
Inlet drying air temperature	37 – 45 °C; Target point is 41 °C	Important for consistent drying results. Lower temperatures take longer for drying to be completed but do not adversely impact product quality; higher temperatures can lead to over-drying of product and erosion of particle size. **Upper temperature limit is regarded as critical.**
Drying time	Not defined	Drying time is dependent on other factors (temperature, air flow, amount of moisture still to be removed from product particles), so drying time is not regarded as a critical control, but drying time will be monitored for information.
Moisture in dried product by in-process NIR measurement	2.0 – 4.0% by LOD	Continuous in-process measurement of water contained in dried product provides accurate assessment of progress of drying operation. **Regarded as critical control to ensure proper drying endpoint is reached.** Final product temperature to be monitored for information.

2. **Continuous Quality Monitoring and Control** for this process uses a probe linked to a nearby NIR spectrometer with a fiber optic probe fitted into the dryer with a compression fitting (see Figure 2). Digital output sent from the dryer control system governs software acquisition of data during processing of a product batch. NIR spectra are obtained every 3 seconds for the duration of drying. For equipment and software information, see Table 2.

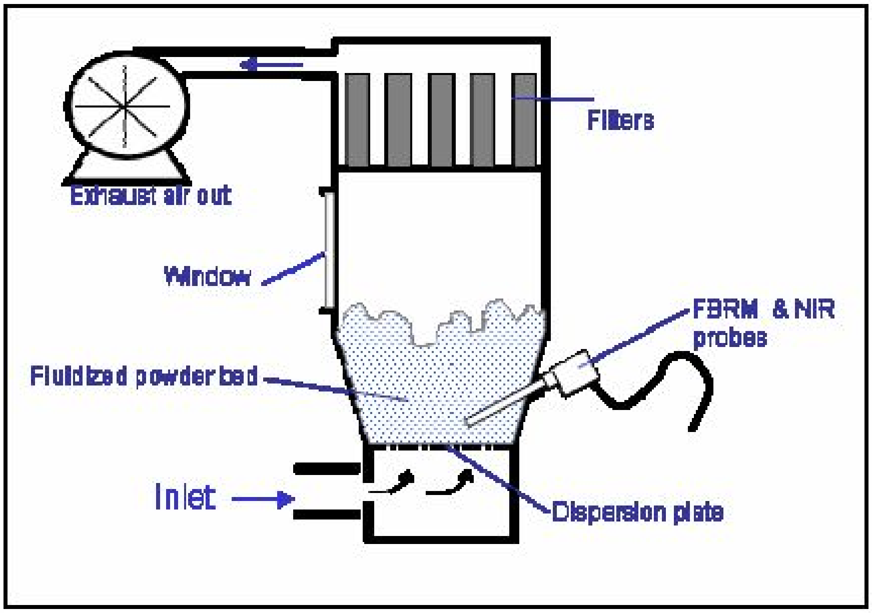

Figure 2. Schematic Representation of Fluid Bed Dryer PAT installation

Table 2. Hardware and Software used for Continuous NIR monitoring of process

Item	Detail
Spectrometer	Sentronic Sentroproc Extended Diode Array NIR spectrometer
Software	Win spec V-7 acc 21.06.2004 software (Sentronic GmbH)
Spectral range	1100 – 2200 nm
Spectral resolution	4 nm
Sample frequency	3 sec
Drift correction	120 min
Reference standard	Spectralon SRS-99
Spectral analysis	Principle Components Analysis using multivariate analysis software (SIMCA P+ v. 10.0.4.0, Umetrics AB, Sweden)

The spectra region 1350 to 2050 nm was used to create a three-factor Partial Least square (PLS) regression model correlated with 51 measured LOD samples taken from a series of production mixtures. The range of LOD measured was from 1.7 to 4.0% (85 to 200% of the 2.0% LOD target). The prediction model (see Figure 3) has an R^2 value of 0.9865 and a standard error of calibration (SEC) of 0.1346. This model was loaded into the spectrometer software and predicts real time moisture content for the dryer (see Figure 4). The spectrometer software outputs this value as an analog signal (4-20 mA) to the control software where a real time trend is displayed on the Operator Interface Terminal (OIT) in the manufacturing area. The dryer control software monitors the process trend and signals the dryer to turn off upon reaching the target moisture content.

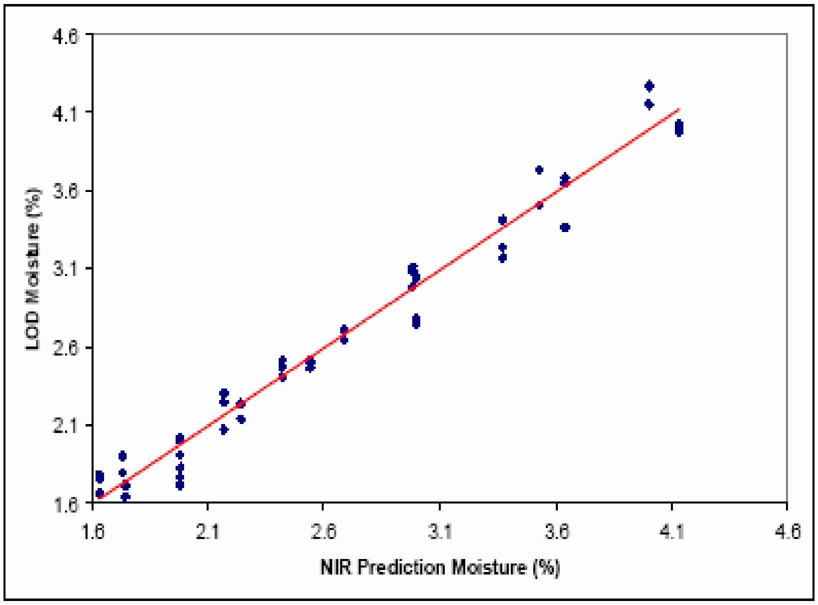

Figure 3. Predicted NIR versus measured LOD

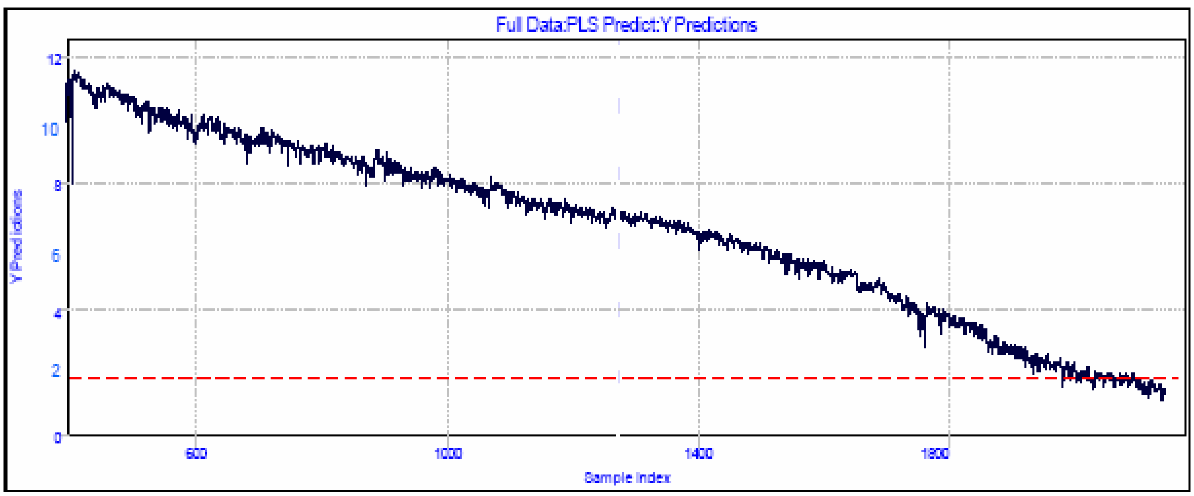

Figure 4. Predicted moisture content of a granulated mixture being dried

3. The **Process Analysis** portion includes examination of conformance or validation batches and a validation report, to be prepared after the conformance batches have been prepared and analyzed. In addition to the usual criteria for product acceptability, equivalence, and consistency, an assessment of drying uniformity may be an appropriate part of the homogeneity analysis of the conformance batches. The PLS regression study used a large number of batches and samples, giving a high R^2 value indicating a strong correlation between the NIR and the corresponding LOD result. This could be used to justify a concurrent validation approach requiring three conformance batches for this first portion of

the process analysis. If a less-established correlation suggests less certainty in the predictive power of the continuous monitoring tool, a larger number of conformance batches may be appropriate to verify the correlation between the on-line control and the desired result.

When a high degree of confidence is established that the continuous in-process monitoring and control of the drying endpoint reliably provides the expected product moisture level, substituting in-process results for end-product testing may be a desirable outcome that could allow discontinuing the end-product dryness testing of the product.

The point where the shift from end-product testing to use of in-process drying endpoint results can be made will depend on the strength of the correlation between the NIR measurement and the product LOD and on proven consistency shown by the process in providing consistent moisture results. With the strong correlations noted earlier for this drying process, it may be possible to make this change during or soon after the production campaign following successful preparation of the conformance batches.