# Process Understanding: Critical for Process Development, Part 1

Ronald D, Snee, PhD; Snee Associates, LLC, Newark, Delaware

A new solid-dose, 24-hour controlled-release product for pain management had been approved but not yet validated because it had encountered wide variations in its dissolution rate. The manufacturer did not know whether the dissolution problems were related to the API, the excipients or to variables in the manufacturing process — or to some combination of these factors.

Frustrated with the lack of process understanding, the manufacturer narrowed the range of possible causes of the unacceptable dissolution rate to nine potential variables — four properties of the raw material and five process variables. The team used a designed experiment (DOE) to screen out irrelevant variables and to find the best operating values for the critical variables (Snee, et al. 2008).

The analysis showed that one process variable exerted the greatest influence on dissolution and that other process and raw material variables and their interactions also played a key role. The importance of the process variable with the largest effect had been unknown prior to this experiment even after more than eight years of development work. This enhanced process understanding enabled the company to define the design space and the product was validated and launched.

This case illustrates the criticality of process understanding. The FDA noted the importance of process understanding when they released “Guidance for Industry: PAT — A Framework for Pharmaceutical Development, Manufacturing and Quality Assurance,” (FDA 2004). The FDA was responding to the realities of the pharmaceutical and biotech industries; namely that pharma/biotech needs to improve operations and speed up product development. Compliance continues to be an issue and risks must be identified, quantified and reduced. The root causes of many compliance issues relate to processes that are neither well understood nor controlled.

The FDA is promoting QbD and Design Space as control strategies to deal with these issues. Fundamental to this strategy is the development of process understanding. The bottom line is that you can’t effectively and efficiently control, improve or transfer a process that you don’t understand. Lack of process understanding leads to delayed schedules, extensive rework and increased cost.

### What is Process Understanding?

The FDA (2004) defined process understanding as “A process is generally considered to be well understood when (1) all critical sources of variability are identified and explained, (2) variability is managed by the process, and (3) product quality attributes can be accurately and reliably predicted over the design space

established for the materials used, process parameters, manufacturing, environmental and other conditions."

Item (3) in this definition relates to prediction of process performance, which requires some form of a model, Y=f(X). In this conceptual model, Y is the process outputs such as Critical Quality Attributes (CQAs) of the product and X denotes the various process and environmental variables that have an effect of the process outputs, often referred to as Critical Process Parameters (CPPs). Models may be empirical, developed from data, or mechanistic, based on first principles.

Models come in two forms: qualitative and quantitative. In qualitative models we typically know the important variables and whether the effects of the variables are positive or negative. In quantitative models we know the important variables and have a mathematical equation that describes the effects of the variables. The quantitative model enables us to estimate the effects of the variables and rank the variables from most important to least important.

For example, McCurdy, et al (2010) developed models for a roller compaction process. Among the models reported was a model in which tablet potency relative standard deviation (RSD) was increased by increasing mill screen size (SS) and decreased with increasing roller force (RF) and gap width (GW). They reported a quantitative model for the relationship:

Log (Tablet Potency RSD) = - 0.15 – 0.08 (RF) – 0.06 (GW) + 0.06 (SS)

Process understanding summarized and codified in the form of the process model, conceptually represented as Y=f(X), can contain any number of variables (Xs). These models typically include linear, interaction and curvature terms as well as other types of mathematical functions.

- At a strategic level, a way to assess process understanding is to observe how the process is operating. When process understanding is adequate the following will be observed:
- Stable processes (in statistical control) are capable of producing product that meets specifications
- Little fire fighting and heroic efforts required to keep the process on target
- Processes are running at the designed speed with little waste
- Processes are operating with the expected efficiency and cost structure
- Employee job satisfaction and customer satisfaction is high
- Process performance is predictable

To assess the state of process understanding at an operational level we need a list of desired characteristics.

**An Operational Definition for Assessing Process Understanding**

The FDA definition of process understanding is useful at a high level but a more descriptive definition is needed; a definition that can be used to determine if a

process is understood at an operational level.

Table 1 lists the characteristics I have found useful in determining when process understanding exists for a given process. First it is important that the critical variables (Xs) that drive the process are known. Such variables are typically called critical process parameters (CPP). It is helpful to broaden this definition to include both input and environmental variables as well as process variables; sometimes referred as the “knobs” on the process.

**Table 1. Characteristics of Process Understanding**

- Critical Process Parameters (Xs) that drive the process are known and used to construct the process design space and process control approach.
- Critical environmental and uncontrolled (Noise) variables that affect the Critical Quality Attributes (Ys) are known and used to design the process to be insensitive to these uncontrolled variations (robustness)
- Robust measurement systems are in place and the measurement repeatability and reproducibility is known for all Critical Quality Attributes (Ys) and Critical Process Parameters (Xs)
- Process capability is known
- Process failure modes are known and removed or mitigated
- Process control procedures and plans are in place

It is important to know the critical environmental variables (uncontrolled noise variables) such as ambient conditions and raw material lot variation can have a major effect on the process output (Ys). Designing the process to be insensitive to these uncontrolled variations results in a “robust” process.

Measurement systems are in place and the amount of measurement repeatability and reproducibility is known for both output (Y) and input (X) parameters. The measurement systems need to be robust to minor and inevitable variations in how the procedures are used to implement the methods on a routine basis. This critical aspect or process understanding is often overlooked in the development process. Gage Repeatability and Reproducibility studies and method robustness investigations are essential to proper understanding of the measurement systems.

Process capability studies involving the estimation of process capability and process performance indices (Cp, Cpk, Pp and Ppk) are useful in establishing process capability. Sample size is a critical issue here. From a statistical perspective 30 samples is the minimum for assessing process capability; much more useful indices are developed from samples on 60-90 observations.

In assessing the various sources of risk in the process, it is essential that the potential process failure modes be known. This is greatly aided by performing a failure modes and effects analysis at the beginning of the development process and as part of the validation of the product formulation and process selected for commercialization.

Process control procedures and plans should be in place. This will help assure that the process remains on target at the desired process settings.  This control procedure should also include a periodic verification of the process model, Y=f(X), used to develop the design space, as recommended in the Phase 3 of the FDA's Process Validation Guidance (FDA 2011).

**Process Problems are Typically Due To Lack of Process Understanding**

Although it is "a blinding flash of the obvious," it is often overlooked that when you have a process problem it is due to a lack of process understanding. When a process problem occurs you often hear "Who did it; who do we blame?" or "How do we get it fixed as soon as possible?" Juran emphasized that 85 percent of the problems are due to the process and the remaining 15 percent are due to the people who operate the process (Juran and Godfrey 1999).

While a sense of urgency in fixing process problems is appropriate some better questions to ask are "How did the process fail?" and "What do we know about this process; do we have adequate understanding of how this process works?"

| Table 2. Process Understanding Leads to Improved Process Performance: Some Examples | | |
|---|---|---|
| **Problem** | **New Process Understanding** | **Result of Improvements Based on New Process Understanding** |
| Batch release takes too long | Batch record review system flow improved. Source of review bottleneck identified. | Batch release time reduced 35-55% resulting in inventory savings of $5MM and $200k/yr cost reduction |
| Low capacity not able to meet market demand | Yield greatly affected by media lot variation. New raw material specifications needed. | Yield Increased 25% |
| Batch defect rate too high | Better mixing operation needed including: methods and rate of ingredient addition, revised location of mixing impeller, tighter specs for mixing speeds and times and greater consistency is blender set-up. | Defect rate significantly reduced saving $750k/yr |
| Process interruptions too frequent | Root cause was Inadequate supporting systems including, lack of spare parts, missing batch record forms and lack of standard operating procedures. | Process interruptions reduced 67% saving $1.7MM/yr |
| Report error rate too high | Report developer not checking spelling, fact accuracy and grammar. | Error rate reduced 70% |

Table 2 summarizes some examples of process problems and how new process understanding leads to significant improvements; sometimes in unexpected areas. Note that these examples cover a wide range of manufacturing and non-manufacturing issues including capacity shortfalls, defective batches, process interruptions, batch release time and report error rates. All were significant problems in terms of both financial and process performance. Increased understanding resulted in significant improvements.

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