Title: **A Continuous Improvement Metric for Pharmaceutical Manufacturing**

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Introduction:

- FDA's Pharmaceutical cGMPs for the 21st Century, A Risk-Based Approach provided the initial momentum needed to help promote collaborative efforts within the pharmaceutical industry. Designed to modernize pharmaceutical manufacturing and make it more efficient, the guidance highlights the importance of continuous improvement to improve efficiency by optimizing processes, reducing variability, and eliminating wasted effort.
- Reducing variability benefits both patients and manufacturers; therefore, regulators have voiced strong support for continuous improvement activities. For example, FDA and the International Council for Harmonization (ICH) support quality-by-design (QbD)-based product development.
- QbD, advanced in ICH Q8 focuses on the use of multivariate analysis in combination with knowledge management tools to understand the impact of critical material attributes and critical process parameters on drug product quality attributes. The heightened product and process understanding that result from using this framework provides a foundation for continuous improvement.
- Statistical methods and novel indices can be used to monitor and benchmark variability, and guide continuous improvement programs in late-stage drug development.

Aims:

Continued Process Verification

- With the implementation of a continued/ongoing process verification program at Stages 3A and 3B of product development, continual assurance is now available to detect any unplanned departures and allow manufacturers to adjust for them. As outlined in regulatory guidance on process validation established by regulatory agencies that include FDA, the European Medicines Agency (EMA), the Pharmaceutical Inspection Cooperation Scheme (PIC/S), and the World Health Organization (WHO), process verification identifies any potential risks and initiates continuous improvement activities when essential, thus helping prevent likely product failures.

Methods:

The Inherent Process Variability, which represents unexplained process variation under current manufacturing conditions, may be expressed by the equation below.

$$\textbf{Inherent Process Variability} = \textbf{Overall Variability} - \textbf{Analytical Method Variability}$$

Once the IPV is calculated for a particular product it can be used to derive a PaCS index. The PaCS index is a derivative of a product's performance measured against a benchmark of similar process. PaCS index empowers management with site specific product performance oversight.

$$\text{PaCS} = IPV_P / IPV_B$$

where, IPV_B is the Benchmark and IPV_p is the Product Inherent Process Variability . A PaCS <1 indicates the process variability is low and a PaCS index > 1 indicates the process variability is high compared to the benchmark. In cases where PaCS > 1, further evaluation may be

required. If IPV_p it indicates that there is an opportunity for reducing process variability of the current product through continuous improvement.
A corporate IPV_B can be established based on dosage form and process

Results:

- Stage 3A batches (including Stage 2 and a predetermined number of commercial batches) is typically used to estimate Inherent Process Variability (IPV) and PaCS index at the initial stages. Contribution of variability due to inherent process represents the process robustness (4M: Man, Machine, Mfg. Method, Material) under current manufacturing conditions.
- Therefore, Inherent Process Variability Contribution (IPV max) = Overall Variability-Analytical Method Variability. PaCS = IPV_P / IPV_B (benchmark)
- A PaCS index greater than 1 indicates the process variability is high, while a PaCS less than 1 indicates that process variability is low compared to the benchmark. Therefore, a PaCS value that is less than 1 is preferred. Because the distribution of the PaCS index is not analytically derivable, confidence intervals can be estimated using Monte Carlo simulation. The PaCS index together with IPV values and the other derived statistics provide a platform upon which further decision making can take place. For instance, high PaCS values would indicate that the process for a specific product is not performing as expected. Estimation of inherent process variability (IPV) allows for determining a PaCS index for the product, and helps in understanding the contribution to variability that comes from the manufacturing process and the analytical method used. In addition, PaCS is a metric developed in relation to the manufacturing process at a particular production site.

Conclusions:

- The index can be effectively used to determine continuous improvement projects at the site. PaCS provided with a tangible quantitative robustness figure for various supply chain decision making. The index can be a component of periodic process performance review by senior management as recommended by ICH Q10.
- PaCS Index may be used to decide such things as who should be primarily responsible for a specific continuous improvement project (i.e., whether process, analytical, or a combination). This is often a point of contention. It could also be used to determine which site has the best PaCS index with respect to a product. This factor will be considered when deciding for or against site product volume increases. In summary, PaCS can provide valuable insight to decision makers, and help to drive continuous quality improvement programs during pharmaceutical development as well as manufacturing.

Keywords:
Continuous Improvement, Metrics, Index