QbD and the New Process Validation Guidance

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Very simply, the aim of pharmaceutical development is to design a quality product and manufacturing process to consistently deliver the intended performance of a final therapeutic product.

To support a final quality assurance approach to manufacturing, it is the information and knowledge gained from pharmaceutical development studies and process characterization studies that lead to an effective quality control strategy, based on scientific understanding.

To that point, in January 2011 the FDA issued its new guidance on Process Validation (PV). The new PV guidance uses the basic principles of scientific understanding put forth in ICHQ8—the foundation of Quality by Design (QbD)—to establish process understanding and link it to product reproducibility. It effectively abandons the old concepts of demonstrating process validation and replaces it with a new, structured approach. It formalizes these principles by describing the level of product and process understanding necessary to satisfy the requirements of Stage 1 of the new PV guidance. To achieve this level of process understanding a framework that integrates product performance as part of process characterization is required. So simply put, the new PV guidance will make it much easier to justify moving toward QbD.

The challenge that many industry personnel face is bridging the gap between the former validation approach of “three batches and we’re done” to understanding how the new PV stages work together to establish process predictability.

In practical terms, the new PV guidance describes the three stages as follows:

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.1

Predictability is the guideword. Pharmatech has established a framework designed to generate the necessary information to satisfy the new PV structure and provide a manageable plan. This framework has been discussed in detail in previous publications and is shown in Figure 1.
Let us focus on Stage 1 - Process Design, because it constitutes the largest change from the classic PV roadmap. This stage is meant to identify and establish a control strategy for the parameters and attributes that affect process predictability and product performance.

**Quality by Design and Process Validation**

The model most commonly purported to embody the principles of QbD is shown in Figure 2.
Figure 2: Quality by Design Model

The key concept in Stage 1 of the new PV guidance and the QbD model links Product Design with Product Performance, as depicted in the inner circle of Figure 2. We will discuss each of these elements within the context of the PV framework and the QbD model.

**Product Design**

All projects begin with a summary of the target product performance attributes that are the foundation of the formulation activity. Understanding the role of each component within the function of the dosage form should include material characterization activities that could influence downstream processing such as particle size, solubility, melting point, bulk density, presence of polymorphs in the drug substance, loaded dose, etc. Ideally, a review of product design should also extend to understanding the basis for the in-vitro product release specifications and any in-process control measurements.

Product design review can be summarized in a risk table capturing the potential impact of each component on the process and product performance downstream. An example of a product performance risk summary is shown in Table 1.
Table 1: Product Design Risk Summary

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>Risk Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Medium</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>Low</td>
</tr>
<tr>
<td>Povidone K-90</td>
<td>High</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>Low</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Medium</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>Low</td>
</tr>
<tr>
<td>Talc</td>
<td>Low</td>
</tr>
<tr>
<td>Ethyl Alcohol</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Process Design-Process Risk Assessment

A process risk assessment is a very effective way to connect the product design, process unit operation and final product performance critical quality attributes (CQAs). In this step a tiered risk assessment approach can be used to identify potential sources of variability before beginning process characterization studies. The risk assessment can be divided into two parts. The first evaluation compares each process step against the defined CQAs to identify which process steps would require close characterization. The second tier of the risk assessment can focus upon the potential impact of the process parameters. Any parameters identified as having a high potential impact on CQAs can be targeted for further study.

Process Characterization: Knowledge Space, Design Space, Control Space

The use of equipment that has been verified to operate in a consistent manner is essential in determining process predictability. While small-scale equipment used in development does not need to be qualified, if the equipment is not predictable, characterization studies will not be reproducible. This should also be applied to any analytical or in-process measurements that will be applied during the development work.

Per the ICHQ8 guidance, the first step in establishing process understanding is to define the knowledge space. The knowledge space constitutes describing the contribution to process stability of the total set of variables for each unit operation across a practical
range of variability. Applying a statistically unbiased approach to process characterization will allow rapid identification of the parameters that affect both process stability and product performance. Commercial process challenges can also be introduced at this stage to limit the variability during scale-up.

At the end of the knowledge space exercise the parameters that have been found to affect process stability and product performance should be evaluated using the same experimental design approach to narrow the process space. ICH refers to this as the Design Space. The ideal Design Space will be one in which the process parameters have no impact on the process stability and product performance. This activity will be critical to establish a Proven Acceptable Range (PAR) for the process.

One challenge with the new guidance is how to determine a defensible sampling and testing plan for the characterization activity. Sampling and testing plans can also be prototyped, evaluated and qualified at small scale in anticipation of commercial scale-up. Industry standards such as ANSI Z1.4-2008 tables can be a good resource for establishing and justifying sample sizes. In some cases, these sample sizes may be too large and other approaches such as performing a power calculation, generating Operating Characteristic (OC) curves and calculating Lot Tolerance Percent Defective (LTPD) to define the consumer risk are effective approaches to making sure you have a sampling plan with sufficient resolution to address the desired producer and consumer risk.

The last step in the characterization program is defining the final Normal Operating Range (NOR) defined by ICHQ8 as the Control Space. The Control space is typically a narrower portion of the Design space that represents the recommended limits that will be allowed in the master batch record.

**Process Design-Validation Master Plan**

With the characterization activities complete the Validation Master Plan (VMP) can be developed to put forth both the rationale, justification and final commitments in terms of moving into Stage 2 of the new PV guidance structure.

**Conclusion**

Applying the basic principles of QbD as defined in ICHQ8 will establish the necessary foundation to satisfy the requirements for process understanding required to meet Stage 1 of the new PV guidance. The framework developed by Pharmatech is a practical roadmap for navigating the application of the principles of ICHQ8 and will identify those parameters which are critical to process stability and product reproducibility. With this foundation of understanding, the process is well positioned to move into Stage 2 of the new process validation guidance that will require final demonstration of process reproducibility at the commercial scale. For organizations that have struggled to get a foothold with QbD, the new guidance will provide the impetus for change if they are to successfully meet the new requirements for process and product reproducibility.

**References**