Chatterjee: How Much is Enough? API Quality Assurance and the New Process Validation Guidance

The challenge all quality professionals face is answering the question, How much is enough?

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The challenge all quality professionals face is answering the question, "*How much is enough?*" Historically we have had the benefit of very prescriptive FDA guidances or industry best practice to fall back on for our validation programs. Today however, we find ourselves in a brave new world where we are the architects of our own reality and potentially our own demise. For quality professionals within the pharmaceutical industry this shift from a prescriptive to descriptive compliance guidance means we have to decide *what is good enough*.

The new Process Validation Guidance has recreated the requirements for demonstrating process predictability into a more extensive program that spans much of the drug development lifecycle. We have discussed how to satisfy the new requirements in this column, and yet there are still ambiguities in the new guidance that encumber the ability of organizations to make the paradigm shift. That things are changing for pharmaceutical and API manufacturers there is no doubt. But, practically, what are we to do about it? It would seem that not even the compliance inspectors from the agency are entirely sure about what is acceptable from an agency perspective.

Quality systems for API manufacturers have always been measured against the standards set forth in ICHQ7A. This includes requirements manufacturers identify as critical process parameters (CPPs) that can affect the product's Critical Quality Attributes (CQAs). However, most best practice focuses on the concept rather than the method of determining the CPPs. Where does that leave us?

The new Process Validation guidance does not point out a method of determining CPPs, just that it needs to be scientifically defensible. So it was surprising to find out from an API manufacturer recently audited by the local FDA office as part of a pre-approval inspection for a new drug filing, that the manufacturer had received an observation because they did not have a clearly defined procedure for determining critical process parameter in their API synthesis process. API manufacturers have always been under scrutiny during the pre-approval process, but the rigor expected by the compliance inspector was surprising and perhaps a portent of things to come.

Keep in Mind

What does this mean in terms of establishing a Quality Management System (QMS) within an API manufacturing operation? I think there are several considerations to keep in mind when evaluating your existing system against these new requirements.

Assess whether you have established a formal framework for risk management as part of your approach to quality. On the pharma side, requiring a formal Failure Modes and Effects Analysis (FMEA) at key stages of the process design, development and automation is rapidly becoming a compulsory element to any defensible QMS. Most API facilities will conduct a Hazard Analysis and Critical Control Plan (HACCP) or a Hazard Analysis and Operability plan (HAZOP). These are effective approaches to manage risk in

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the process and in the product and have been mandated in FDA guidance for some regulated markets, such as for Seafood processors. Many FDA inspectors have limited exposure to these techniques but are familiar with FMEAs. Standardization is another way to build a comfort level that risk is being a managed in the process design.

Establish a policy and procedure for process characterization that is based upon sound scientific principles. The approach does not need to be overly prescriptive but approaching the process design the same way a pharmaceutical customer would approach a drug process will make it easier to explain and defend to a compliance inspector. CQAs for an API could be broadened to consider attributes that may have an impact on the drug CQAs. For example, polymorph evaluation through X-Ray Powder Diffraction, glass transition and melting point curve establishment through Differential Scanning Calorimetry and impurity detection can go a long way to linking the CPPs and CQAs of the API process to the Critical to Quality (CTQs) of the pharma process.

Develop subject matter expertise that pertains to establishing sample size and sampling plans. The ability to defend or justify the sample locations, frequency and quantity are guaranteed to be part of any question regarding CPPs or process validation.

I would *invest in building statistical analysis capability within the organization.* The new process validation guidance is looking for evidence of objective analysis that clearly states the risk of drawing an erroneous conclusion. This means being able to quantify the inspection risk associated with sample size and accept/reject criteria, the alpha and beta risk from statistical analysis associated with process capability assessments and the confidence intervals around each analysis. Together these summarize, in quantitative terms, the likelihood of non-conforming material being released as part of an accepted lot.

The last component is to *include on-going monitoring of CPPs and critical output parameters* found to be essential in ensuring process predictability as part of an overall program for demonstrating process predictability.

Building Confidence

Many of the main issues pharma is struggling with today involve characterization. This is where API manufacturers may have an advantage if they have implemented a Process Analytical Approach (PAT) for key processes in the manufacturing step.

The three stages that comprise the new definition of process validation may not be as directly or easily applicable to API manufacturing: this would depend on whether process development is started at small scale and other factors. Rather than just mapping to the steps in the new guidance, it is more important to consider how the outputs from each stage correlate to the argument that the process is predictable and validated. Doing this in a consistent manner will go a long way to building confidence that the systems and practices of the development, quality and manufacturing group are geared toward ensuring process stability and reproducibility.

In terms of defining and demonstrating product quality, there is no doubt that the rules are changing. The largest paradigm shift for both Pharma and API Quality Assurance may be the revelation that API manufacturers must now consider pharma process validation requirements as part of their quality system, thus changing the risk assessment component of any Supplier Qualification activity significantly.

Aligning thinking for an API manufacturer to that of a drug manufacturer can be done to a great extent through policy and procedure. For some manufacturers, documenting the development and characterization activity is the biggest departure from current practice. Whether the additional rigor can be implemented without impacting the standard cost of the API remains to be seen. It certainly raises questions regarding China's and India's ability to continue to deliver as low a cost API to the global

marketplace as they do today. However, if they are able to make the transition in quality thinking, API manufacturers will be able to meet the requirements of the new process validation guidance and the FDA without compromising their commitment to the requirements of ICHQ7A for the rest of the world.

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