Process Validation Review: How Many Ways can you bake a Pie?

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If you're like me, you cook for Thanksgiving. In my family, I'm expected to make several pies, and my favorite is Kentucky Pie, a cross between chocolate chip and pecan pie-- yummy! Every year it turns out different. Some years I make it with bourbon, some without, and sometimes with cornmeal instead of flour, sometimes with different types of chocolate. Each time it's pretty good but different because I like to be creative. What has that to do with process validation (PV), you ask?

Basic process controls in baking are attained with a recipe, a batch record for us in the Pharma industry. But even with a recipe and controlling all the inputs (in the pie case, eggs, pecans, chocolate, flour, butter, other good stuff), the chocolate is a little different each time (I like Belgian dark) and the pecans could be from different harvests and the eggs are from different farms. So even if I use the same recipe, same type of pie tin and the same oven, each pie is a little different, but also very close. We could say at this point, we have OK *process control* (recipe and same amounts) but no true consistency (different quality/type of starting materials) and no *process validation*. The variation of the ingredients and oven temp, etc. can be thought of as the "design space" for our pie, as long as it passes QC (me and my family's high standards!). Therein lies the basis for process validation--proving consistent quality batches once process controls are in place.

Likewise, for a given process and drug product (DP), there are many process inputs and process variables (WFI, salts, reaction time, temperature, process hold times and the like) but only one DP which must meet specifications each and every time. To have confidence that we can produce drug substance (DS) or DP batches consistently at scale, regulators, including FDA, require a demonstration of that ability (scientific evidence), a.k.a., process validation.

But do we really need PV in the pharma industry, since each batch is tested and therefore meets all quality specifications? That is a good and logical question which many folks have considered. The answer lies in the notion that you cannot "test quality into" a product, but rather we would like to "design quality into" the product, also called Quality by Design. The other part of the answer has to do with level of assurance/confidence which is what validation is all about-- validation drastically increases our confidence/assurance that a process is repeatable, and this is important with drugs/biologics where the value is high and the downside of product failure is also high.

In my pie case, given time, and consistency of materials (ok-- and the same recipe!), and an experienced taste test panel, I could demonstrate that I could make good Kentucky Pies consistently. But how many would I have to bake to convince you that I can do a good job repeatedly? Maybe 3 or 4? 5 or 6? Thus the question of how many batches to run for PV comes up. I have to convince my test panel, day in and day out, that I can

make yummy pies consistently that are within our "design space" for appearance, taste, texture, flaky crust, size, etc.

When I'm not baking, I work mainly with biologics, and as you know, biologics have *inherent variability*, so in process validation our goal is to understand that variability and its influence on product quality. In order to do a good job with process validation then, we must understand the process; we must have good *process knowledge*. Once we have good process knowledge (from lab studies for columns or from clinical manufacturing or other studies), we know what process variables are important and which are less important. This can also be done with a parameter risk assessment. In this stage we also need to understand *process capability*, the expected variation of a parameter.

Then when we have both process knowledge and have some information about process capability, we can complete full scale "conformance batches" or "PPQ" batches (process performance qualification). It's important to gather and record all of the in-process data and parameters used from these validation batches as well as the end test results. Ideally, descriptive statistics are used to evaluate (or at least record) the variation.

The number of PPQ batches chosen varies across product type and complexity and the chosen statistical confidence desired. For example, for a cell therapy product where each unit is a batch, gathering process data from 22 may be appropriate where 22 cell therapy batches are processed daily. For a full scale batch of a monoclonal antibody three batches may be sufficient, and for an orphan drug where only one batch is made every two years, we may have to rely on one batch along with two others from clinical manufacture. In each case the number of batches used for process validation should be justified with a rationale, and one must show that the process produces a consistent output, meeting all of the quality attributes, given the expected variation of process parameters. Thus in each case, one must have *data to support* the claim that the process consistently produces a quality product meeting all of its quality attributes/specifications.

One time when I was doing an audit of a plasma facility, I asked about the color of the plasma units--some were slightly pink while most were straw colored. I was told that this is a natural variation across different donors and there is no quality impact. This is a good example of variability in biologics which has no impact once the plasma is pooled and processed (in this case to IGIV). In PV language we would say that the plasma color is neither a key process parameter nor a critical process parameter.

Another time I was working with a crystallization process and it was fascinating to watch a single seed crystal initiating complete crystallization in the solution, but only if the salt was at the saturation concentration, but not below saturation (we would call this (% salt in solution or mg/mL) a critical process parameter in PV language).

PV is multidisciplinary and typically includes input from R&D, Engineering, Tech Transfer, Pilot Scale studies, and production for full scale batches. This is one reason most people consider PV somewhat complex. It's important to have input from these groups when writing PV protocols. It can also be helpful to have an outside technical person or consultant to review both the protocol and the report before submission to a regulatory authority or prior to a preapproval inspection.

Two good resources that I recommend for PV are the FDA guidance--Process Validation: General Principles and Practices (Jan 2011) and PDA Tech Report No. 60.

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Also, numerous recipes for Kentucky Pie can be found online!