Critical Process Parameters and Critical Quality Attributes: Why Does the Selection Process Take so Long?

Quick, can you name the top 10 Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) of your bio-pharmaceutical manufacturing process? Well if you hesitated don’t feel bad. Most pharmaceutical process validation and engineering professionals could probably only list three or four of each for products that they should be intimately familiar with. The awareness, understanding and integration of these central concepts by Process Validation professionals is only now taking root. Are these new terms or concepts that most of us are not familiar with? Have you read the 2011 Food and Drug Administration (FDA) Guidance for Industry on Process Validation? How can the early (or retrospective) development of your process control strategy help?

New Terms And Old Concepts

It is not difficult to intuit what the process parameters are for most units of a manufacturing process. Generally they involve temperature, time, flow rates, pressures,
and numerous other discreet input settings or output readings on the process equipment that are employed in a manufacturing process. But what is the criticality of each of those process parameters? Certainly, do not expect a regulatory agency to answer that question for you. Biopharmaceutical firms that have developed their manufacturing process are expected to have conducted the necessary experimentation, whether employing a design of experiments methodology or some other strategy, to have documented the parameters which are critical, key or non-key to drive their process. Similarly, the attributes that the active pharmaceutical ingredient (API), bulk drug substance, or final formulated drug product is purported to possess in terms of biological activity, composition, identity, purity, and performance are quality attributes that must be firmly understood, tested for, and documented by the manufacturing firm. These attributes are not to be simply in-process or release tests used during routine operations but rather parameters that pose higher risk and are indicative of process and product variations.

**The FDA Guidance On Process Validation**

The FDA Guidance for Industry – Process Validation: General Principles and Practices—although published in January of 2011, has only been read by less than 5% of process engineering and validation professionals (informal survey conducted by this author). The 19-page document co-written by the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Center for Veterinary Medicine (CVM) is a well-crafted, quick read that is a must for all industry professionals. The guide very effectively lays out the statutory and regulatory requirements for process validation but better yet offers recommendations and general considerations for the same. Three Stages: Process Design, Process Qualification, and Continued Process Validation are delineated. The establishment of the Process Parameters and Quality Attributes, whether they are critical, key, or nonkey, should be established at the Process Design stage or before.

**“Developing” Robustness Early**

The process parameters that a firm should investigate and document are many, and a design-of-experiments approach may prove helpful to determine their criticality and boundaries to which the manufacturing process can be acceptably run. In reality, the product development scientist first developing clinical entities may be the first source of parameter and variable information. Through numerous refining experimental iterations, the range of CPPs and CQAs may be honed to those that require robust testing at the Process Qualification Stage. The proper documentation of these process parameters and quality attributes may not exist for some products that have long been in the commercial manufacturing stage. For those firms, a concerted reverse engineering effort may immediately be required in order to determine and document all process parameters and attributes reported to regulatory agencies as being possessed by the product. Subsequently, historical data mining and statistical analysis of the same should render evidence of those parameters and quality attributes demonstrating a critical level of control to the process and safety and efficacy to the product. The sooner a manufacturing firm has this process control strategy data available and agreed upon by their cross functional team of subject matter experts, the sooner the firm can conduct a gap assessment and subsequent process re-qualification where deemed necessary.
In sum, the strong knowledge of your manufacturing process’ CPPs and product’s CQA will provide immediate and critical measures of the control or variability of the process and product. Moreover, a firm and its process technical staff, as well as the quality assurance professionals should educate themselves on the details of those CPPs and CQAs in order to minimize their variation. The new FDA guidance on these principles, although issued over two years ago, is still a mystery to those whose professional career is to implement the same in their manufacturing facilities. The need for well established, existing manufacturing processes to possess a comprehensive process control strategy clearly identify the critical process parameters and critical quality attributes is as necessary and expected as for those beginning the process today. Investment in process knowledge is critical for both patient and corporate good health.

Learn more about ProPharma Group’s Cleaning Validation services. Contact us to get in touch with Alfredo and our other subject matter experts for a customized Cleaning Validation solution.