CASE STUDY

Life cycle in process validation. Continued
Process Verification
ABSTRACT

This article presents the concept of life cycle applied to process validation and how this idea was already underlying the first FDA reports on the challenges that the pharmaceutical industry had to face in the 21st century.

It explains the three stages of validation that are distinguished, under different names, both by the FDA in its new 2011 validation guide and the EMA in its 2014 guide, and in Annex 15 of the GMPS of March 2015.

The strategy to be followed for the implementation of Stage 3 of Continued or Ongoing Process Verification is looked at in depth. For those products validated under the traditional approach before March 2015 (legacy products), the fact that it is also necessary to develop a Continued Process Verification (CPV) or Ongoing Process Verification (OPV) protocol has been emphasised. For these products, we present a case study on implementation that Telstar's Consulting Division has developed for a wide variety of products (including solid, liquid, semi-solid and sterile products) for a major pharmaceutical company.

1. Regulatory environment

In August 2002, the FDA launched the initiative Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century with the objective, among others, of promoting the adoption of technological advances in the pharmaceutical industry and facilitating the application of modern systems quality management from the point of view of Risk Management. This initiative culminated in the 2004 report where they outlined the challenges that the pharmaceutical industry had to face for the century that was just beginning.

In this 2004 FDA report, it was indicated that achieving and maintaining a state of control for the production process begins at the process development phase and continues throughout the commercial phase, thereby sketching out the product's life cycle. It was stated that relying only on three full-scale production batches prevented knowledge of the complete history, clearly indicating that with three batches it is not possible to get to know all the sources of process variability and that, therefore, it is very difficult to have the process "under" control.

Also in 2004, as part of the initiative that began in 2002, the FDA issued Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance which promoted the development and implementation of PAT (Process Analytical Technology) to be used in the design, analysis and control of production processes through real-time measurements of critical material attributes and critical process parameters.

As we can see, 16 years ago, concepts were mentioned that little by little have materialised during the following years in different guides and GMP regulations and which, even more slowly, if possible, are being implemented in the pharmaceutical industry.

Between 2004 and 2009, the International Conference for Harmonization (ICH) published the ICH Q8 guide (Quality by design – Pharmaceutical Development) and the ICH Q9 guide (Quality Risk Management) which focus on the scientific basis applied to the development of products and on risk management as a fundamental tool in the different stages of the drug life cycle, and the ICH Q10 guide where the concept of control strategy were defined.
In 2011, the new FDA Validation guide *Guidance for Industry: Process Validation: General Principles and Practices* came out, which replaced the already old 1987 guide and which reflected some of the objectives of the above-mentioned FDA initiative for the 21st century. This guide aligns the concepts of process validation with those of the product life cycle and the concepts already indicated in the ICH Q8-Q9-Q10 trilogy.

In Europe the process validation requirements also reflect the life cycle principle and are basically defined in two documents. The 2014 *EMA guideline on process validation for finished products – Information and data to be provided in regulatory submissions* which establishes the validation requirements in stage 2 of the product life cycle (see section 2) and in the new version of Annex 15 of the 2015 GMP that focuses on stage 3 (continued process verification).

### 2. New approach to process validation

The process validation ceases to be considered as an isolated event to be carried out prior to the launch of the product on the market and becomes related, from the point of view of the life cycle, with the development of the product and the process linking it with maintaining the process in a controlled status during commercial production.

The new approach to process validation embraces three phases, compared to the traditional or historical approach. This three-phase approach is valid both in Europe and with the FDA, with only minor differences in terminology and detail; for example, the greater level of emphasis on statistical principles or the more detailed subdivision of the phases in the FDA guidelines. Some of these differences will be discussed during the course of this article (see figure III).

This new approach, based on science and risk management, combines the knowledge acquired during the product development phase with a structured study of process performance and a product quality monitoring system in order to demonstrate that the process remains controlled throughout the product life cycle.

It is intended to take advantage of the knowledge and information acquired, either from the development phase in the case of new products, or from the experience of years of production for existing products 1 (legacy products), so that the patient's requirements are transferred to the attributes of the product. This requires production processes to be defined with a control strategy that ensures that these attributes are met.

Ultimately, process validation must demonstrate the suitability and robustness of the control strategy and must provide continuous assurance that the process remains in a state of control.

The objective is to control the process with high levels of confidence, knowing all the sources of variability and to understand how variability in the critical material attributes and critical process parameters affects the critical quality attributes. This requires time and experience, aspects that are clearly not met if we only focus validation on three full-scale production batches prior to the launch of the product.

### Fig. II. The three phases of process validation, according to the FDA and the EMA

### Fig. III. Summary of the main similarities/differences between the FDA and EMA process validation guidelines
Figures II and III show the three phases of validation according to the FDA and EMA, outlining the main objectives of each phase.

The most important points of each phase are presented below in summary form.

### 2-1 Phase I

The objective of this phase is to generate sufficient knowledge of the process (through the design of experiments, multivariate analysis, etc.) to establish the relationships between the Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) which allow the control strategy to be defined. The Quality Target Profile (QTTP) is used to establish the CQAs (see figure IV).

### 2-2 Phase II

This is the phase that in traditional terminology embraced the entire concept of process validation. The FDA, always more precise and detailed, names this stage as Process Performance Qualification (PPQ) and divides it into two sub-phases, 2.1 and 2.2 (see figure II). Phase 2.1 consists of the qualification of all equipment, facilities and systems that are part of the process and which must logically be qualified before carrying out the Process Qualification. The same requirement must be met for Europe, even if it is not explicitly divided into this sub-phase.

Phase 2.2 is what, in the terminology prior to this change, was called Process Validation in its entirety. In Europe, as described in Annex 15 of the GMPs, it can be done in three ways:

1. **Traditional process validation**

   Manufacture of a number of batches of finished product under routine conditions to confirm its reproducibility. It is considered acceptable to perform it with a minimum of three consecutive batches, although it is stated that this initial validation exercise involving three batches should be completed with additional data obtained from subsequent batches, as part of the on-going process verification program.

2. **Continuous process verification**

   A Quality by Design (QbD) approach, where it has been scientifically proven during the development phase that the established control strategy provides a high degree of assurance of product quality.

3. **Hybrid approach**

   A hybrid of the traditional approach and continuous process verification.

The FDA does not carry out such a division and establishes that a Process Performance Qualification (PPQ) must be carried out, in which, among other aspects, the number of batches should be justified to demonstrate with a high degree of assurance that the process is able to consistently provide a quality product, considering an acceptable level of confidence in both intra-batch and inter-batch variability.

Whichever method is used to carry out this phase, the third phase is obligatory: Continued Process Verification in FDA terminology (CPV) or Ongoing Process Verification (OPV).

### 2-3 Phase III

During this phase the quality of the product must be monitored to ensure the state of control is maintained throughout the product life cycle with an evaluation of the relevant tendencies in the process.

Figure V indicates the steps to follow and figure VI outlines the road map for a CPV/OPV protocol.
This phase usually begins with a risk analysis that, depending on whether a new or existing product is being analysed, will contain:

1. **New Products**: Analysis of the results of the previous phases (Phase 1 and Phase 2), with a study of the variability in the different CQAs due to the CMAs and CPPs. The suitability of the control strategy defined in Phase 1 is reviewed and the sampling level for each parameter/attribute (increased or decreased) is defined with respect to the previous phases.

2. **Existing Products** (legacy products): Criticality study of the different quality attributes (QAs), Material Attributes (MAs) and Process Parameters (PPs) in order to deduce the control strategy (see Case Study).

Subsequently, a protocol called CPV or OPV (initials of Continued Process Verification or On-going Process Verification) must be carried out, which defines and covers the following points:

1. **Monitoring**. A monitoring programme for the relevant parameters to be recorded must be defined, specifying frequency and establishing how and with which system this data will be acquired. Knowledge of the process is key to determine what to monitor and at what stage, to ensure process variability is detected which could increase risk for the patient. The Monitoring Plan does not have to be the same for all products or for all measurements of a given product.

2. **Data analysis**. When, how and by whom it is to be carried out must be defined.

3. **Actions**. What actions will be carried out if any of the parameters do not meet the established criteria must be defined.

4. **Implementation**. How this new element, which is the Continued Verification Protocol, will be integrated into the existing Quality System of pharmaceutical companies must be defined.

In short, continued process verification is a permanent activity that constantly monitors the manufacturing process, reacts to changes and identifies opportunities for improvement.

### 3.- Existing products

For existing products, whose validation was carried out before the new process validation requirements established by the EMA in March 2015 (legacy products), the new approach continues to apply but by going directly to the third stage (3.2 according to the FDA, see figure II), through a protocol of Continued Process Verification (FDA nomenclature) or Ongoing Process Verification (EMA nomenclature).

These products were developed at the time with a level of understanding of the process and a definition of the control strategy appropriate to the regulation of the time, but in many cases, not sufficient for current regulatory expectations and industry standards. On some occasions a systematic classification of process parameters was not developed in order to define a CPV programme. In other cases, there are gaps in the process data as they were not collected for the important attributes and parameters that are necessary for a CPV programme.
The methodology is the same as in Phase I, replacing the knowledge acquired when developing the process with the experience and knowledge acquired during the commercial phase (PQR inputs, non-conformities, change controls, stability, information from technology transfer, etc.).


The purpose of this project was to develop and implement a series of stage 3.2 programmes (see figure II) of continued process verification for different products. Figure VII shows the method followed.

For each product or product family, the following steps were performed:

- Division of the process into unit operations or process steps
- Identification of critical quality attributes (CQAs)
- Analysis of those raw material attributes that affect the critical quality attributes, thus obtaining the critical material attributes (CMAs)
- Analysis on the different steps of the process of those process parameters which affect the critical quality attributes, thus obtaining the critical process parameters (CPPs)
- Establishment of the control strategy
- Continued verification of its suitability and adjustment, as all sources of variability and their impact on critical quality attributes are known.

In the following sections, this method is explained for one of the products on which the CPV/OPV protocol was performed.

4-1 Steps / Unit operations of the manufacturing process

One of the first points in approaching the identification of process attributes and parameters, is to divide the manufacturing process into stages and identify the materials (APIs, excipients, etc.) involved in each one. Figure VIII shows the unit operations identified for the manufacturing process of the case study product:

4-2 Identification of critical quality parameters (CQAS)

Based on the quality attributes (QA) of the product, a risk analysis was performed to determine if the attribute is critical or not (CQA = Critical Quality Attribute, nCQA = Non-Critical Quality Attribute). The risk analysis was based on:

- Severity that a variation in the quality attribute affects the safety/efficacy of the product
- Knowledge of the value of severity. This parameter expresses whether or not there is confidence in the value assigned to the severity, based on the historical data of the product and on knowledge of it. For example, if there is little information about the product, the level of knowledge of the severity value is low. If, on the contrary, there is a large amount of historical information (information from previous lots, PQR inputs, non-conformities, change controls, stability, information from the transfer of technology, etc.), the level of knowledge and certainty of the severity value is high.

In the case at hand, it was a product that had been marketed for several years and, therefore, a large amount of information was available, so it was considered that the level of knowledge of the assigned severity value was high.
Identification of critical material attributes

Once the CQAs of the product were determined, the Critical Material Attributes (CMA) were established.

A risk analysis was performed, where for each CQA identified in the previous section, the Material Attribute (MA, see row figure VIII) related to that CQA was determined, and then whether that material attribute was critical or not (CMA = Critical Material Attribute, nCMA, Non-Critical Material Attribute) based on:

- Impact of that Material Attribute on the CQA
- Knowledge basis for determining that impact. As in the previous section, this parameter expresses whether or not there is confidence in the value assigned to the impact, based on the knowledge of the product.

Identification of critical process parameters

For each process step, the process parameters (PPs) were listed and their impact on each of the CQAs was evaluated, to determine if they were Critical Process Parameters or not (CPP = Critical Process Parameter, nCPP = Non-Critical Process Parameter) based on:

- Impact of that Process Parameter on the CQA
- Knowledge basis for determining that impact. As in previous sections, this parameter expresses whether or not there is confidence in the value assigned to the impact, based on the knowledge of the product.

Determination of the control strategy

Once all the CQAs, CMAs and CPPs were identified in each process step, a summary matrix was completed which related each CQA with its CMA and the corresponding CPPs in the different process steps.

The control strategy was established from this matrix by conducting a Failure Mode and Effect Analysis (FMEA) for each of the critical parameters (CMA and CPP) that affect each CQA. These parameters must be kept within the established ranges to ensure compliance with the CQAs.
5.- Conclusion

The evolution of process validation has been presented in this article, which has gone from being considered an isolated event that took place prior to the launch of a product and which was partially reviewed in the PQR, to a permanent activity which, during the life cycle of the product, constantly monitors the manufacturing process, reacts to changes and identifies opportunities for improvement.

The final aim is always the same: to demonstrate with a high level of certainty that the process is able to consistently provide a quality product, considering an acceptable level of confidence in both intra-batch and inter-batch variability. For this, it is necessary to continuously monitor the process to get to know all the sources of variability that allow it to be under control.

To achieve this aim, the FDA in its new 2011 validation guide, the EMA in its 2014 guide and Annex 15 of the GMPS of March 2015 divide the validation into three stages, which have been explained in this article.

The third stage has been looked at in depth, defining the path to follow for the implementation of a continued verification protocol (CPV or OPV) needed for products that will be launched to the market after the new validation requirements as well as for existing products (legacy products) validated prior to these requirements.

A practical example of implementing a continued process verification protocol (CPV or OPV) for an existing product has been shown, where the critical parameters that allow the establishment of the control strategy were defined, based on knowledge of the product acquired during the commercial phase.

References

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