



SHORT COMMUNICATION

# Increased importance of the documented development stage in process validation <sup>☆</sup>

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**Abstract** Current trends in pharmaceutical quality assurance moved when the Federal Drug Administration (FDA) of the USA published its new guideline on process validation in 2011. This guidance introduced the lifecycle approach of process validation. In this short communication some typical changes from the point of view of practice of API production are addressed in the light of inspection experiences. Some details are compared with the European regulations.

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## 1. Introduction

Pharmaceutical production has to fulfill two main requirements without fail: to meet the expectations of customers and, on the side of authorities, production has to meet GMP regulations, which have the force of law. “GMP” refers to Good Manufacturing

Practice (see e.g. ICH Q7A, 2000) that requires numerous activities in order to protect, in turn, the consumer from purchasing a product that is not effective or – even worse – dangerous. That means manufacturers and packagers of drugs, veterinary medicines and medical devices need to take proactive steps to ensure that their products are safe, pure, and effective. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate cases of contamination, mix ups, or any other errors. GMP regulations are often mentioned as “current”, i.e. “cGMP” expresses that manufacturers must employ technologies and systems which are up-to-date to comply with the regulations.

## 2. Continuous development for better quality

The concept of quality is rather complex, since it includes both chemical–technological aspects and strategic business considerations. As a consequence of the technical evolution and the competitive economical environment, the pharmaceutical industry has been going through fundamental transformation in the recent decade (see e.g. Alt, 2003). These conditions forced pharmaceutical producers, for instance, to elaborate customer-oriented strategies in order to know how to fulfill needs and expectancies,

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and to handle complaints in a proper manner (Alt, 2003; Süller-Faigl, 2007).

The introduction of information technique (IT) in the management was also advantageous, since computerized systems can make data collection, handling and archiving easier. Suitable software packages are available in the market to obtain a well-designed basic process for the effective use of management resources and to improve the efficiency of an enterprise. The goal is integrating information across the company and to analyze the whole set of data for shaping a comprehensive business plan and strategy for the company. Such system is for, e.g. the well known SAP (System, Application, Product in Data Processing), and specifically the quality module of the software that can be operated in accordance with the cGMP regulations (Süller-Faigl, 2007). For instance, supplier qualification and the whole process of logistics and quality control of incoming raw material can also be integrated into the system.

Moreover, the producers are expected to maintain such quality system that is able to develop itself, i.e. to “learn” from the recognized mistakes. Therefore different systems were introduced to serve these purposes. As such the well-known CAPA system (Corrective Action and Preventive Action), under which the handling of process deviations, out-of-specification results, observations of self-inspections and of external audits (see e.g. Fields, 2008), etc. can be coordinated. Similarly, the Change Management System has to ensure that uncontrolled or concealed changes cannot occur in the technology that may affect the quality of the product.

As it can be seen from the general trends, the development of technical-informational background of pharma companies and the expectancies of customers and/or authorities are in interaction with each other: while tools become more effective and sophisticated, the company requirements are also harder and very often the approach of a given process also becomes more complex. The publication of the new FDA guidance (FDA, 2011) fits into this progress.

### 3. New aspects of validation activities

According to the corresponding ICH (International Conference on Harmonization) guide (see ICH Q7, 2000, 12.40) “process validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes”. However, in 2011 the FDA guidance states that “process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product”. In the new context the PV activities are divided into three stages:

Stage 1: *Process design*: that means the collection of data and gaining knowledge during development and scaling up experiments.

Stage 2: *Process qualification*: evaluation and confirmation of the designed process, establishing of scientific evidence that the process is reproducible, “quality both within a batch and between batches” (FDA, 2011) is assured. Actually, the activities of this stage are almost equivalent with the earlier PV activities (see also Pluta, 2011).

Stage 3: *Continued process verification*: it is the assurance of that the production process remains in the state of control during the entire period of the routine production.

That means, while in 1987 the FDA emphasized the validation protocol, testing, the results and the corresponding documentation; according to the 2011 lifecycle approach, the validation activities start immediately in the development stage and continue throughout the whole commercial life of the product (see also Pluta, 2011). In practice, the number of processes run depends on the complexity of the process, etc. The expectation of ICH Q7 (ICH Q7, 2000) is similar: “For prospective and concurrent validations, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g. complex API processes or API processes with prolonged completion times).” After declaring the process validated in the PV report, the validation activity is finished according to the “old” concept.

It was also stated in 1987 by the FDA: “This guideline is issued under Section 10.90 (21 CFR 10.90) and is applicable to the manufacture of pharmaceuticals and medical devices. It states principles and practices of general applicability that are not legal requirements but are acceptable to the FDA.” That means actually, that the previous guideline did not discuss PV of API production itself, only the PV of final products and medical devices was discussed.

In the light of the 2011 guide: quality cannot be adequately, or merely assured by in-process and finished-product inspection or testing. The development of the process and of the product, the demonstration of process conformity and the maintenance of the validated, controlled state of the production are integrated into a single complex aspect. Ultimately, it is expected from the producer that each step of a manufacturing process has to be controlled to consistently assure that the finished product meets all quality attributes included in the specifications.

It has to be noted that this concept is not really new to the USA either as it was pointed out by Pluta (2011) (see also Evans, 2000). It is also in line with the ICH recommendation for building up suitable PV program (ICH Q7, 2000, 12.5) that requires periodical evaluation to verify that the process still operates in a valid manner (see also Hiyama, 2011). Moreover ICH Q11, Step 3 (2011) has allowed: “As an alternative to the traditional process validation, the continuous process verification can be utilized in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle” However, the coherence of life stages of a product became emphasized in 2011 by FDA.

### 4. The role of development as a part of the validation activities

Already in 2003, the ICH issued “A New Vision for Ensuring Product Quality” that addressed a “harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science” (see e.g. Hiyama, 2011; ICH Q8, 2009; ICH Q9, 2005; ICH Q10, 2008). In this approach also the (transferred) knowledge forms the basis for the manufacturing process, *control strategy*, PV approach and ongoing continual improvement. (ICH Q10, 2008 3.1.2).

According the FDA's view on PV (FDA, 2011) it is understood that Stage 1 is generally described as "process understanding". Every following activity is based on the information collected in the development stage.

A fundamental step before PV is to recognize the critical steps and parameters of the production process that influence product quality. It is because manufacturers have to understand and detect occurring variations. The sources, presence and degree, impact of variations should be identified, and suitable control has to be established. The early process design does not have to be conducted under cGMP, but decision and justification of controls are made in form of reviewed documents.

In practice, critical parameters have to be established based on true scientific justification through the course of quality risk analysis. The role of R&D is to deliver data for risk analysis in the form of detailed development reports. Thus, risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data are needed to demonstrate the desired high level of assurance of commercial process robustness (see e.g. Hiyama, 2011; Pluta, 2011). For reliable work in this stage, the collaboration between R&D and manufacturing function is crucial. As Hiyama (and many other authors) pointed out, "for innovative PV approaches, technology development and senior management support are required" (Hiyama, 2011).

The new FDA guide issued in 2011 states that "the terms *attributes* (e.g. quality, product, component) and *parameters* (e.g. process, operating, equipment) are not categorized with respect to criticality". The reason for this statement is explained by the next sentence "the perception of criticality as a continuum rather than a binary state is more useful", since risk based decisions are expected throughout the lifecycle of PV. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated every time when new information becomes available. It is also important to keep in mind that the degree of control over attributes or parameters should be commensurate with their risk to the process and process output, i.e. for attributes or parameters posing higher risk, higher degree of control is appropriate. The final goal of PV is still homogeneity within a batch and consistency between batches.

## 5. Conclusions

The changing attitude of regulations and authorities often requires the re-establishment of the strategy of quality management and, in line with this fact, even the re-thinking of the

organization structure of quality assurance or allocation of human resources may be necessary. The quality has to be built into the product already from the stage of design thus the importance of archived documents (i.e. development reports) from the stage of development, even in case of old, known and well-managed technologies became pronounced. Development experiences have to be properly documented and handled as an extremely important source of knowledge in solving further technological problems since it creates the scientific justification and knowledge source of every further activity in and for production.

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