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Validation – a brief introduction

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Abstract. The process validation was developed in the 20th century in order to improve the quality of pharmaceutical products. The validation concept has expanded over the last 50 years from analytical methods used to control pharmaceutical substances to analyses of computerized systems. Validation is nowadays successfully used in most areas. The validation of a method aims to ensure the effectiveness of the method from the point of view of some statistical parameters during each stage of production and not only at the end of the process. By validation, scientific evidence is established that a process is capable of consistently delivering quality products. It is also recognized internationally that validation of a product is required in any production process of a new product.

Keywords: *validation, prospective validation, retrospective validation, simultaneous validation, correlation study*

1. INTRODUCTION

The concept of validation was first proposed in the mid-1970s by two FDA (Food and Drug Administration) officials, Ted Byers and Bud Loftus, in order to improve the quality of pharmaceutical products (Agalloco 1995 quoted in Sarvani *et al*., 2013).

It was proposed as a direct response to the large volume of problems of parental sterility products. The first validation activities focused on the processes involved in making these products, but they spread rapidly across all pharmaceutical production processes (Keyur *et al*., 2014).

The purpose of validation is to test the quality of the system at each stage and not only at the end, as validation activities include checks on production materials, operating procedure, training of the persons involved and monitoring of the system during production (Sarvani *et al*., 2013).

U.S.F.D.A (United States Food and Drug Administration) pioneered the validation process concept, but until September 29, 1978, the definition of the validation process did not appear in any of the U.S.F.D.A. literature, no CGMPs (Current Good Manufacturing Practices) law has spoken about the validation process (Chapman K.G, 1991 quoted in Keyur *et al*., 2014). The validation concept has expanded over the past few years in a wide range of activities, from the methods of analysis used to control the quality of medical substances and drugs to computerized systems, the validation process has become an important and integral part of CGMPs (Kaur *et al*., 2013).

Validation is a method with applicability in various fields: medicine, sales, economics, psychology, chemistry, biology, etc. In fact, the validation concept can be applied in most areas.

Validation of a new or improved method must ensure the integrity and quality of the method in terms of precision, accuracy, detection limit, limit of determination, selectivity, linearity field, and last but not least the transferability of the method (Cardone, 1983; Miller, 1991; Alexandrov 1996).

Process validation can be defined as "establishing documented evidence that provides a high degree of assurance that a certain system of equipments and processes that are consistently

linked meet approved specifications and produce products with predetermined quality attributes" (Lakshmana, 2014).

The word validation means "*evaluating validation actions or proving effectiveness*" (www.processvalidation.com). Process validation can be defined as collecting and evaluating data from the product design phase and throughout the process, which establishes by scientific evidence that the process can consistently deliver quality products. (Sarvani *et al*., 2013).

Table 1 *Definitions of the validation notion (after Keyur et al., 2014)*

Institutions	Definition
European Commission, 1991	Validation – "Act of proving in accordance with GMPs that any ..." process actually leads to expected results (Nash, 1993).
European Commission, 2000	"evidence that this process, operated within established parameters, can perform efficiently and reproducibly to produce a drug substance meeting its predetermined specifications and quality attributes" (Potdar, 2009).
US FDA	"The process validation is the establishment of evidence to ensure a high degree of certainty for a specified process to consistently produce a product that meets its predefined specifications and documented quality characteristics." (FDA, 1998).
ICH	"Process validation represents the means of ensuring and providing supporting documents specifying their design parameters by whom they are capable repeatedly and reliably produce a finished product of the required quality."(ICH, 2011).
WHO	"The documented document proving that any procedure, process, equipment, material, activity or system can lead to the expected result."

Process validation can also be defined as the collection and evaluation of data, from the process design stage, which establishes scientific evidence that a process is capable of consistently delivering quality product. (Keyur *et al*., 2014).

Validation is an essential part of good manufacturing practices (CGMPs). It is, therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. (WHO, 2006).

Validation represents the action to verify that any process, procedure, activity, material, system or equipment can achieve the desired results. (Rachna *et al*., 2012).

Process and systems validation is fundamental to achieving the goal of using a new product. For this purpose, the results of a large number of measurements are analyzed either by the paired t-test or by regression analysis. Regression analysis is the preferred statistical method in such cases because it is less restrictive and provides a greater amount of information, unlike the t-test (Massart *et al*., 1988; Miller *et al*., 1988).

From a statistical point of view, validation involves assessing the relationship between one or more predictors using a performance criterion. The fundamental objective is to predict the values of the criterion based on predictor(s) values. Assuming their values are of a quantitative, continuous nature, the most used indicator of validity is the correlation coefficient (Pearson), referred to in this context as the coefficient of validity (Popa, 2011).

Finding a correlation between a predictor (eg, SAR measurements) and a certain criterion (eg, GNSS measurements) is not sufficient to support the conclusion that higher LOS (Line of Sight) values for GNSS measurements are the effect of a higher LOS level for SAR measurements, but only that the two variables tend to vary simultaneously with one another (Popa *et al*., 2011).

Validation principles can be synthesized in the following words: quality, safety and efficacy in the design *and* building of a product. Quality cannot be adequately assured merely by in-process and finished-product inspection. Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes. (Keyur *et al*., 2014; WHO, 2006).

Analyses of the validation concept also appear in the articles Chao and Forbes, 2003; Trubinski, 2003, Ahir *et al*., 2014; Parashar *et al*., 2013; Chaitanya *et al*., 2005; Kathiresan and Kiran, 2005; Varshney *et al*., 2013; Rockville,2010; Dashora and Singh, 2005. These articles present the main features of the process validation in the pharmaceutical industry.

2. TYPES OF VALIDATION

Depending on the type and timing of validation, the following types of validation can be distinguished: prospective or perspective validation, concurrent validation, retroactive or retrospective validation and revalidation (Sarvani *et al*., 2013; Lakshmana, 2014; Keyur *et al*., 2014; Chaitanyakumar, 2005).

Prospective validation represents all the activities performed before the distribution of new products to ensure compliance with the initial (legislative/proposed/etc.) conditions by the product's characteristics. (Sarvani *et al*., 2013; Lakshmana, 2014). Prospective validation is defined in Keyur *et al*., (2014) article as the documented evidence that a system does what it purports to do.

Concurrent validation is issued for establishing documented evidence during actual imputation of the process to show that the process is in a state of control (Sarvani *et al*., 2013).

Retrospective process validation is based on a review of historical manufacturing and testing data, and the analysis of accumulated results from past production to assess the consistency of a process. It is assumed that the composition, procedures and equipment remained unchanged. During retrospective validation results of in-process and final control tests are evaluated. All difficulties and failures recorded are analyzed to determine limits of process parameters and product-related problems. As retrospective validation is not considered to be a quality assurance measure it should not be applied to new processes or products. (Lakshmana, 2014; Keyur *et al*., 2014).

Revalidation is exploratory review of the current performance of the validation effect to confirm the validated status of the facilities, systems, equipments, manufacturing processes and software. Revalidation is necessary for the products that need to be reviewed in time. (Lakshmana, 2014).

3. PROCESS VALDATION STAGES

Process validation involves a series of activities taking place over a lifecycle of the product and process (Keyur *et al*., 2014).

Activities related to validation studies can be classified into three stages: the pre-qualification phase or the qualification phase; process validation phase (Process Qualification phase); continued process verification or validation maintenance phase.

This pre-validation phase or the qualification phase covers all activities related to product research and development, formulation pilot batch studies, transfer of technology to commercial scale batches, establishing stability conditions and storage and handling of in-process and dosage forms, equipment qualification, operational qualification and process capacity. (Sarvani *et al*., 2013).

"It covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, operational qualification, process capability. Also, this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process" (Keyur *et al*., 2014).

During the procedure's validation phase (Process Qualification stage) the process design is evaluated to determine if the process is capable of commercial manufacturing. (Keyur *et al*., 2014).

In this stage it is checked if all established limits of the critical process parameters are valid and if satisfactory products can be produced even under "worst case" conditions. (Sarvani *et al*., 2013).

There are two aspects of process qualification: (Keyur *et al*., 2014)

• Design of facilities and qualification of equipment and utilities. Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.

• Process performance qualification. Part of the planning for stage 2 involves defining performance criteria and deciding what data to collect when, how much data and appropriate analysis of data. Manufacturer must scientifically determine suitable criteria and justify it. Objective measures, where possible.

Continued process verification or validation maintenance requires frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process and that all stages have been followed, including change control procedures. At this stage the validation team also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. (Sarvani *et al*., 2013).

A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation and the attributes susceptible of the variation. (Keyur *et al*., 2014).

Elements of validation are: (Sarvani *et al*., 2013):

Design qualification (DQ): It is a documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.

Installation qualification (IQ): There are verified all the aspects of a facility, utility or equipment that can affect product quality

Operational qualification (OQ): There are verified all aspects of a facility, utility or equipment that can affect product quality

Performance qualification (PQ): There are verified all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

From the methodological point of view, the validation analyses start from the structure of the problem, namely from the identification of the general objective, the derived objectives, the identification of the necessary factors in the analysis. A second phase in the process validation consists in the standardization of each factor for their compatibility and then they can be hierarchized according to the importance they represent for the main objective.

4. STATISTICAL PROCESS VALIDATION CONTROL

Statistical process control (SPC) includes, according to Lakshmana *et al*., (2014): sampling plan, experimental design, variation reduction, process capability analysis, process improvement plans.

SPC will not improve a poorly designed product's reliability, but can be used as a tool to maintain the consistency of how the product is made.

Sampling must represent the batch under analysis. Statistical quality control criteria as a condition of approval and release of batch must meet its predetermined specifications. (Nash, 2003).

Statistical parameters for use in validation are the following (Zamosteanu *et al*., 2008):

accuracy; precision: intermediate precision and reproducibility; detection and quantitation limit; linearity and linear range; selectivity and working range.

The linearity of an analysis technique is its ability (within a given range) to obtain test results that are directly proportional to the sum of the sample to be analyzed. To determine whether there is a linear dependence between the two sets of data, calculate the correlation coefficient.

The linearity range is the range between the detection limit and the maximum level of the measured series parameter (concentration, LOS, etc.) of the linearity.

Acceptance criteria: the value of the correlation coefficient should be in the range of 0.990 - 1, which shows that, in the studied range, the dependence between the two elements is linear (Zămosteanu *et al*., 2008).

The Pearson correlation coefficient is the indicator of the linear relationship between the variables. As a result, the Pearson correlation value decreases when the linear model does not adequately describe the relationship between the two elements (Sackett and Lievens, 2008).

The conditions for calculating the Pearson correlation coefficient are: random sample, distribution variables that do not deviate severely from normal distribution (this is all the more important as the sample is smaller).

To illustrate this problem, linear and curvilinear correlation can be calculated (Popa, 2011).

The interpretation of the validity coefficients without explicit verification of the linearity condition is one of the quite frequent mistakes in the validation studies (Seymour, 1988).

For this purpose, the scatter-plot plot can be used, or specialized procedures can be used to estimate the association of the variables (eg, in SPSS program: Analyze/Regression/Curve Estimation).

In statistical analyses, particular attention must be paid to aberrant values, the presence of which may have unexpected effects on the value of the correlation coefficient. The value of the correlation coefficient is strongly influenced by the existence of pairs of aberrant points. A good alignment of some extreme values can greatly increase the value of the correlation coefficient for two weakly correlated variables, and a good correlation can be "destroyed" by the weak alignment of some extreme values.

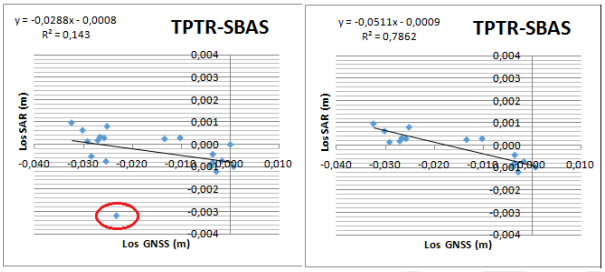

***Figure 1**. The effect of the extreme (bivariate) values on r on the data set representing the LOS values obtained for the TPTR permanent station*

Methods for detecting residual values:

Univariate (via charts with boxes). Everything outside a reference area is a residual value. Bivariate. Points dispersed in a trusted ellipse, 95%; all that is outside the trust ellipse is a residual value.

Multivariate (Mahalanobis D2 distance). The Mahalanobis distance is the distance between a P point and a D distribution. (Mahalanobis, 1936).

5. CONCLUSIONS

Validation refers to the establishment of documented evidence that a process or system can effectively and reproducibly produce a product with identical or similar characteristics. In its short existence, about 50 years, validation has proven its worth in various stages of the manufacturing process, for the preservation, improvement of products and even the use of new methods.

Validation has become a very important research topic when using new products that produce similar results to old ones. Today validation is used in various industries, research, medicine, etc. Also, the validation process is closely related to the development of technology (softwares, computers, tools to collect the data needed).

Validation involves the collection and evaluation of data, throughout process stages, which establishes scientific evidence that a process is capable of consistently delivering quality similar to the one with which the correlation study has been done. The use of validated methods is important for a researcher to demonstrate the qualification and competence of a new product. This implies prospective or perspective validation, concurrent validation, retroactive or retrospective validation and revalidation.

Activities related to validation studies can be classified into three stages: the pre-validation phase; process validation phase and validation maintenance phase, and can be done by statistical process control.

Like any new type of analysis, they also have their limitations. One of them is that validation of a product is directly dependent on obtaining a common element between the validated product and the one used as the reference product. There are also areas where validation must have the same zero point (eg, Geodesy).

REFERENCES

Agalloco J., Validation: an unconventional review and reinvention, 49(4), 2011, 175-179.

Ahir KB, Singh KD, Yadav SP, Patel HS, Poyahari CB (2014) Overview of Validation and Basic Concepts of Process Validation. Scholars Academic Journal of Pharmacy 3: 178-90.

ALEXANDROV, Yu I. Analyst, 121, 1996, p. 1137.

CARDONE J.M.J. Assoc. Off. Anal Chem, 66, 1983, p. 1257.

Chaitanya Kumar G, Rout RP, Ramtake S, Bhattacharya S. Process Validation, The Indian Pharmacist, 2005, 14-19.

Chao AY, John Forbes F (2003) Prospective process validation Pharmaceutical process validation (3rd edn), Marcel Deckker, NY, USA.

Chapman K. G: A History of Validation in the United States, Part I, Pharma Technology. November 1991; 39-98.

Dashora K, Singh D; Validation- The Essential Quality Assurance Tool for Pharma Industries. www. pharminfo.net. 2005; 3: 45-47.

FDA Guide on APIs, 1998, 48. PIC Guide, 1999, 32.

ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities), May 2011EMA/CHMP/ICH/ 425213/2011 ICH/ Committee for medicinal products for human use (CHMP), pg. no- 13.

Kathiresan K, Kiran K (2005) Basis of validation-Pharmaceutical Prospective (1 edn), K.K. Publishers, Chidambaram 32-46.

Kaur H, Singh G, Seth N; Pharmaceutical Process Validation: A Review. 2013; 3 (4): 189-194.

Keyur B. Ahir, Khushboo D. Singh, Sushma P. Yadav, Hetal S. Patel, Chetan B. Poyahari, Overview of Validation and Basic Concepts of Process Validation, Sch. Acad. J. Pharm., 2014; 3(2): 178-190.

Lakshmana Prabu S, Suriyaprakash TNK, Ruckmani K, Thirumurugan R (2014) Concepts of Process Validation in Solid Dosage Form [Tablet] – An Overview. SAJ Pharma Pharmacol 1: 103. doi: 10.18875/23752262.1.103

Mahalanobis, Prasanta Chandra (1936), "On the generalised distance in statistics", *Proceedings of the National Institute of Sciences of India* ***2*** *(1): 49–55,* Retrieved 2012-05-03.

MASSART D.J., VANDEGINSTE B.M.G. DEMING S.N., MICHOTTE Y. si KAUFMAN L., Chemometrics, A Textbook Elsevier, Amsterdam, 1988, p. 88.

MILLER J.N., Analyst, 116, 1991, p. 3.

MILLER J.C. si MILLER J.N., Statistics for Analytical Chemestry, Horwood, New York, 1988, p101

Nash R. A., Wachter A. H: In Pharmaceutical Process Validation. Third Edition; Revised and Expanded, Marcel Dekker Inc., New York, 1993.

Nash RA, Wachter AH (2003) Introduction: Pharmaceutical process validation. (3st edn).

Parashar B, Gupta R, Khurana G (2013) A review on process validation as an essential Process. International Journal of Research in Pharmaceutical Sciences4: 226-9.

Popa Marian, Validitatea de criteriu a testelor de personalitate: limitari și soluții statistice, A XI-a ediție a Conferinței Naționale de Psihologie Industrială și Organizațională "Al. Roșca", 7-8 aprilie, 2011, București,

Potdar MA; Pharmaceutical Quality Assurance. 2nd Edition, Nirali Prakashan, 2009: 8.6-8.20.

Rachna Pandita, A C Rana, Nimrata Seth, Rajni Bala, Introduction & general overview of Pharmaceutical process validation, International Research Journal of Pharmacy IRJP, Volume 2012; 3(6): 60-64.

Rockville MD; Guideline on General Principles of Process Validation. U.S. Food and Drug Administration, U.S. FDA: 2010.

Sackett, p.R. and Lievens, F. (2008) 'Personnel selection'. Annual Review of Psychology 59, 419-450.

Sarvani V, Elisha Raju P, Sreekanth Nama, Leela Madhuri Pola, Chandu Babu Rao, PROCESS VALIDATION: AN ESSENTIAL PROCESS IN PHARMACEUTICAL INDUSTRY, Sarvani V. *et al.* / IJMCA / Vol 3 / Issue 2 / 2013 / 49-52.

Seymour Richard J., M. ASCE and David Castel, Validation of Cross-Shore Transport Formulations, 21st International Conference on Coastal Engineering June 20-25, 1988 | Costa del Sol-Malaga, Spain.

Trubinski CJ (2003) Retrospective validation: Pharmaceutical process validation (3rd edn), Marcel Deckker, NY, USA.

Varshney P, Shah M, Patel P., Rohit M (2013) Different aspects involved in process validation. Innovare Journal of Science 1: 16-9.

WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO technical report, series no. 863-34 th report, Annex 6 – GMP: Guidelines on the validation of manufacturing processes: 4-7.

WHO Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 937, 2006 – Annex 4 Supplementary guidelines on good manufacturing practices: validation.

Zamosteanu Nina, Raport ştiinţific, AMINELE BIOGENE-IMPLICATII IN PATOLOGIA UMANA, Grant TD 282/2008.

