

Review Article

MODERN FDA GUIDANCE AND COMPARATIVE OVERVIEW OF FDA AND EMA ON PROCESS VALIDATION

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ABSTRACT

This article explains the new guidance, what is different from the old standard FDA Guidance and provides a comparative overview of FDA and EMA draft guidance, the key changes in relation to the previous guidance and reviews its potential impact on the current industry approaches to science and risk-based design and qualification activities which support the process validation program.

In 1987, the U.S. Food and Drug Administration released General Principles of Process Validation, the first-ever guidance standard on process validation in the life sciences field. As part of its 21st Century Initiative, last year FDA introduced a draft of Process Validation: General Principles and Practices, which throws the 1987 guidance out the window and moves directly to the forefront of modern validation theory. On April 12, 2012, EMA (European Medicines Agency) published a new draft for the process validation GMP guideline. The new guideline will supersede the current Note for Guidance on Process Validation that came into practice on September 2001. Many are unfamiliar with some of the concepts in the draft, including risk assessments, statistical methods, formally planned and documented engineering studies, and especially ongoing and never-ending process metrics.

Keywords: FDA, EMA, Process Validation, Guidance

INTRODUCTION

This article traces the comparative overview of Food and Drug Administration (FDA) and European Medicines Agency (EMA) on process validation based on some documents. The Food and Drug Administration is an agency of the United States Department of Health and Human Services, and also one of the ancient comprehensive consumer protection agencies in the U.S. Federal government. The FDA is responsible agency for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), and veterinary products. FDA and EMA, which have been closely collaborate the development of standards [1]. The European Medicines Agency (EMA) is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for importance in the European Union. The agency provides regulatory instruction and guidance to manufacturers to assist with the valuation of such medicines. When comparing the EMA guidance with the US FDA document, it is clear that the EMA does not assist its guidance to be directly analogous to the USFDA guidance. The overview of FDA and EMA in process validation is the goal of this article; it is also a comparative overview [2]. Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products [3].

DISCUSSION

Modern FDA guidance

Now a day, technologies are changing our world. We live in a globalized world. We see many changes in the world based on explosion of knowledge and capabilities. Because of this reason, we face many problems in food and drug safety. So FDA faces critical challenges in public health. The Food and Drug Administration (FDA or USFDA) is a branch of the United States Department of Health and Human Services, one of the United States federal executive

departments. The USFDA is responsible for ensuring the safety and effectiveness of products. The responsibility of USFDA is to protect the people from unsafe food, drugs and other medical products. And also make sure consumers have access to accurate information about the products [4]. New FDA guidance is different from the old standard FDA guidance. Some of the most significant changes include in these guidelines are:

- Highlights is a new section to provide immediate access to the most important prescribing information about risks and benefits
- Easy reference is a table of contents to detailed safety and efficacy information
- the date of initial product approval, making it easier and faster to determine how long a product has been on the market
- Internet reporting and toll-free number information for suspected adverse events, to encourage more widespread reporting of side effects. Other minor changes include the acknowledgement of some concepts which have gained wide acceptance in industry including:
- Integrated team approach – the guidance strongly recommends input in the validation process from a wide range of disciplines, as well as the full support of senior management.
- Process Analytical Technologies (PAT) – the guidance introduces PAT concepts and gives guidance on the role it can play in process validation.

The most notable change is the addition of a summary outlining the important information about a product, clearly displayed at the top of the page. Designed to help health care professionals find the information they need quickly, Highlights will typically be half a page in length and will confer a concise summary of information about specific areas including: Boxed Warning, Indications and Usage, and Dosage and Administration. The addition of a new Patient Counseling Information section places greater emphasis on the importance of communication between patients and health care professionals. This new section is designed to help health care

professionals declared their patients about important limitations and uses of medications. It also will serve as a guide for discussions about the potential risks involved in taking a correct treatment and steps for managing those risks. If the FDA has honored patient information for a prescription drug, it will be printed at the end of the label immediately after the Patient Counseling Information section or will accompany the label so it can be shared [4].

Many guidelines are there in Food and Drug Administration; some of them are included in this article. Some of the modern FDA guidelines are Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. When the manufacturing of sterile drugs and biological products using aseptic processing this guidance is intended to help manufacturers meet the requirements in the Agency's current good manufacturing practice regulations. Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, this guidance is used to evaluate out-of-specification (OOS) test results. The OOS results includes all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer is the purpose of this document. Quality Systems Approach to Pharmaceutical CGMP Regulations: In order to implement modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) this guidance is helpful for manufacturers. The guidance describes a comprehensive quality systems (QS) model, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. In full compliance with parts 210 and 211, the guidance explains how manufacturers implement such quality systems. Process Validation: General Principles and Practices: This guidance consist of the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances), collectively referred in this guidance as drugs or products. This guidance incorporates principles and approaches that all manufacturers can use to validate manufacturing processes. Botanical Drug Products : This guidance explains when a botanical drug may be marketed under an over-the-counter(OTC) drug monograph and when FDA regulations require approval for marketing of a new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. These all are the current view point of FDA. These all Guidance are relates to the validation of Human and veterinary medicinal products, biological and biotechnological products and active ingredients.

Comparative overview of FDA and EMA on process validation

The EMA operates under the EU with about 700 employees headquartered in London. Purpose of this EMA is to evaluate the medicinal products. Funding comes from company fees when they submit applications (75%) and the 27 member states (25%). centralized and decentralized are the two paths of Pharmaceutical companies to bringing drugs to market. The EMA is a single coordinating body for drug safety and quality. Main responsibilities of FDA and EMA are the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. These two agencies want to expand the public's knowledge of medicines, medical devices, and cosmetics. EMA is roughly parallel to the U.S. Food and Drug Administration (FDA), but without FDA-style centralization. In March 2012, the European Medicines Agency (EMA) released an initial draft version of a new guideline on Process Validation. That document follows the recent update to the USFDA Guidance on Process Validation, and brings the EMA guideline into line with ICH Q8, Q9 and Q10. Comparison of USFDA guidance and EMA guidelines is mainly based on this initial draft version of a new guideline on process validation document. This document is intended as guidance. The guidance document gives a deep idea about the future direction for process validation. The USFDA guidance released in 2011 is much prescriptive than the EMA document. The USFDA document is a useful reference for the manufactures that follows traditional process validation [5][6]

Process Validation

According to FDA guidelines In1978, "A validated manufacturing process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing through the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, personnel), but it also includes the control on the entire process for repeated batches or runs."In 1987, "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics" [7].

In January 2011, "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" [8][9].

The guidelines on general principles of process validation mention Options: Prospective process validation (also called premarket validation), Retrospective process validation, Concurrent validation and Revalidation. In prospective process validation, an experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put into commercial use. Most validation efforts require some degree of prospective experimentation to generate validation support data. This particular type of process validation is normally carried out in connection with the introduction of new drug products and their manufacturing processes. The retrospective validation option is chosen for established products whose manufacturing processes are considered stable and when on the basis of economic considerations alone and resource limitations, prospective validation programs cannot be justified. Concurrent validation is a subset of prospective validation and is conducted with the intention of ultimately distributing product manufactured during the validation study. Concurrent validation is feasible when nondestructive testing is adequate to verify that products meet predetermined specifications and quality attributes. Re-validation provides the evidence that changes in a process and/or the process environment, introduced either intentionally or unintentionally, do not adversely affect process characteristics and product quality [10] [11] [12].

According to EMA guidelines Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes. Continuous process verification (CPV) has been introduced to cover an alternative approach to process validation based on a continuous monitoring of manufacturing performance. This approach is based on the knowledge from product and process development studies and / or previous manufacturing experience. CPV may be applicable to both a traditional and enhanced approach to pharmaceutical development. It may use extensive in-line, on-line or at-line monitoring and / or controls to evaluate process performance. It is intended that the combination of the guidance provided in the note for guidance on development pharmaceuticals (CPMP/QWP/155/96) and the note for guidance on pharmaceutical development (ICH Q8R2) together with this guidance should cover all of the critical elements in manufacturing process for a pharmaceutical product for human use [13]. For veterinary medicinal products, the applicable guidance is that provided in the note for guidance on development pharmaceuticals for veterinary medicinal products (EMEA/CVMP/315/98) together with this guidance [14]. Although the ICH Q8 guideline is not applicable to veterinary medicinal products the principles detailed in this guideline may be applied to veterinary medicinal products should an applicant choose to apply an enhanced approach to pharmaceutical development.

In order to come with traditional process validation the manufacturer should perform a minimum of three validation batches at product commercialization and if it is successful make the product routinely in the future without further consideration to

process validation. When the product is launched successfully the validation effort dies. The key aspect of the ICH guidelines (Q8, Q9 & Q10) is the concept of product life cycle. The US FDA guidance, the EMA document does not break down validation lifecycle into stages. Three stages described by USFDA (product development, process qualification, continued process verification) can be applied to the EMA guidance [15] [16].

Stages of USFDA

USFDA Stage 1- Product development: EMA guidelines specify the design space, CPV and pilot scale production to assist with product understanding and development of validation strategies. USFDA stage 2- process qualification: This stage mainly focus on traditional validation and also EMA guidelines only permits this traditional approach. But they offer the approaches such as CPV and hybrid and they provided some expectations also. USFDA Stage 3- continued process verification: Continued process verification is the ongoing monitoring through statistical analysis of batch data, non-conformances, customer complaints and similar product quality feedback mechanisms of the validated state of a process. The goal of the third validation stage is continual assurance that the process

remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability [6].

Who is affected the changes?

If the products like human drugs, veterinary drugs, biological and biotechnological products are sold in EMA regulated markets, the manufactures will be directly affected by the alteration. But the medical devices and Active Pharmaceutical Ingredient (API) manufactures are not directly affected because the guidance may contain useful information for such activities. The manufactures in other non-EMA PIC/S regulated markets are indirectly affected. The EMA have close alignment with PIC/S which means that PIC/S may adopt the guidance in full. Manufacturers of the following product types are specifically excluded from the scope of the guidance. Where alternative guidance or regulation is used by the FDA, it has been specified in table 1.

Table 1: Alternative Guidance [4], [5]

Product type	Relevant guidance/regulations
Type A medicated products (articles and feed) for animal use	NA
Medical devices	Global Harmonization Task Force SG3/N99-10:Quality Management Systems – Process Validation Guidance ed. 2 (2004)
Dietary supplements	NA
Human tissue	FDA Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation (March 2002)

Key changes in new guidance

As per the 2001 note, the updated guidance has essentially the same scope. The intent is to provide advice on what to consider for dossier submission for market authorization and, by implication, determine appropriate process validation strategies for commercial dosage forms. As per the 2001 edition, the draft guidance is a substantially

different document. The new guidance formulated the life cycle concept for process validation and aligns with ICH Q8, Q9 and Q10. It also pays its attention on non standard method of manufacture. It also provides scope for flexibility of approach, utilizing traditional methods, CPV or combination of both. There is little difference between the requirements of the old and new guides, as illustrated in the table. 2

Table 2: Differences between the requirements of the old and new guides [4], [5]

1987 guide	2011 guide
Describes "Installation Qualification" which, in practical terms, refers to IQ, OQ and arguably equipment PQ. The 1987 guide does not mention OQ or equipment PQ.	Describes "Process Performance Qualification" which, in practical terms, refers to equipment PQ (if not previously covered) and prospective process validation batches.
Describes "Equipment Qualification" which, in practical terms, refers to IQ, OQ and equipment PQ.	Describes "Process Performance Qualification" which, in practical terms, refers to prospective process validation batches.

Comparison of USFDA and EMA

The comparison of EMA guidance and US FDA document, it is clearly say that the EMA does not intend its guidance to be directly analogous to the US FDA guidance. There are many similarities in the US FDA document not covered by the EMA guidance and there are some important differences between the documents. Incorporation into validation practices of product life cycle, quality risk assessment and efficient quality system practices as described in ICH Q8, Q9 and Q10. Significant emphasis on continued process verification through analysis of pre and post release data to provide confidence of an ongoing valid process. There should be an acknowledgement and provision of scope to emerging processing technologies, such as PAT to assist the validation effort. Enhanced detail to provide understanding of regulator expectation on what constitutes an appropriate validation effort. These are the similarities when compared the EMA guidance and USFDA document [4].

For marketing, the process validation needs minimum number of batches. The US FDA guidance states that the number of batches must be sufficient to provide statistical confidence of the process. The EMA draft guideline states "a minimum of three consecutive batches", with justification to be provided. Some exceptions are there in this statement. The significant emphasis on documenting the product development phase as part of process validation in the USFDA guidance. The EMA document encourages the use of the product development activities, but is less prescriptive on requirements. Specifically the EMA guidelines allow using of CPV to replace traditional validation efforts. This is a significant variation from the US FDA approach, which does not place high emphasis on CPV, and requires all three stages of process validation to be fully addressed, regardless of whether contemporary or traditional methods are utilized. The process validation definitions are different in EMA guidance and US FDA document. The EMA definition: "documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a

medicinal product meeting its predetermined specifications and quality attributes." it is the long established definition. The USFDA document redefined this definition as "the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product." it is a documentation exercise [5]. Many other notable issues are there in USFDA guidance and EMA guidelines. The development and execution of process validation activities are assisted by USFDA guidance. The EMA guideline is a guide for what to consider when developing process validation strategy for dossier submission. The USFDA guidance considers equipment and process design, as well as equipment qualification as part of the overall process validation effort. The EMA guideline sees process as independent from equipment and facility. Currently, the EMA still relies on Annex 15 of the GMP guide for instruction on equipment qualification. It is likely that Annex 15 will be updated in the near future to reflect the changes in process validation guidance [4] [5].

CONCLUSION

FDA and EMA are the agencies to protect and promote of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. These two agencies want to expand the public's knowledge of medicines, medical devices, and cosmetics. FDA and EMA, which have been closely collaborate the development of standards. The new FDA guideline is different from old standard FDA guidance. Process validation is not as a one-off event. A life cycle approach should be applied couple product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production, stated EMA. Guidance is intended to apply to data build to validate the manufacturing process of the intended commercial dosage form only. It is not directly relevant to the manufacture of the active substance or other starting materials, although it may contain information useful for such activities. It is intended to apply to medicinal products for human and veterinary use. Guidance for Industry – Process Validation: General Principles and Practices are the current inclination in process validation; this Guidance describes process validation as an integral part of a product's entire life cycle.

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