



Process Validation of Tablet Dosage Form in Industries

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ABSTRACT

Effective process validation contributes significantly in assuring drug quality. Quality is always an imperative prerequisite when we consider any product. Validation is one of the important steps in achieving and maintaining quality of the final product. Validation is a fundamental segment that supports to a commitment of company towards quality assurance. It also assures that product meets its predetermined quality specification and quality characteristics. Validation of individual step of manufacturing is called as process validation. Process validation is the key element to assure the identity, strength, purity, safety, efficacy and maintaining the quality of final product. By validating each step of production process we can assure that the final product is of best quality. This review gives an introduction about validation, overview about process validation and its importance in the manufacturing of tablet dosage form.

Keywords: Quality, Process parameters, cGMP

INTRODUCTION

In the 1970s, there was a series of contamination issues in large-volume parenteral bottles that, with a handful of other significant adverse events, led regulatory authorities and manufacturers to focus more on process understanding and quality assurance. The idea that finished product testing was not enough to assure product quality began to grow. Industry needed a better system to determine whether a product was "good".¹

In the mid-1970s, FDA's Ted Byers and Bud Loftus began to promote the idea that a focus on process design and an evaluation of support processes and functions would assist in assuring that processes were under control (rather than just "testing quality into the product"). At a 1974 conference, Byers called this new predictive approach "Design for Quality".¹

In 1987, at the request of industry, FDA published its original guideline on *General Principles of Validation*. The agency established a more formal approach to process validation and created the assertion that multiple batches need to be run. This concept eventually translated into the three-batch approach, where the successful running of three consecutive product batches represents a validated process.¹

Tablets are solid dosage forms that contain medicinal substances with suitable excipients manufactured by direct compression of powders or granules with the application of high pressures, using steel punches and dies. Tablets can be of any size, weight, colour and shapes, and may have surface markings. Tablets can also be film-coated and/or have imprints.²

Validation is an important part of good manufacturing practices (GMP). Hence it is an integral division of the quality assurance department 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 and Quality, safety and efficacy must be designed and built into the product. Validation of processes and equipment's is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifications.³

World Health Organisation (WHO) Definition- Establishing documented evidence, which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes.³

United States Food and Drug Administration (US FDA) Definition (1987) - Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.⁴

United States Food and Drug Administration (US FDA) Definition (2011) - 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.⁵

European Union (EU) Definition- The 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.⁶

The new guideline published in January 2011 by FDA, in its own words, "Aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonization (ICH) guidances for industry, Q8 (R2)



Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System. Although this guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.”⁷

Regulatory Requirements for Process Validation⁴

FDA regulation describing current good manufacturing practices (cGMPs) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The cGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the cGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100 (a), which states that “here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess”.

The cGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§ 211.160 (b) (3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)).

The cGMP regulations also provide norms for establishing in-process specifications as an aspect of process validation. Section 211.110(b) establishes two follow when establishing in-process specifications.

The first principle is that “in-process specifications for

such characteristics [of in process material and the drug product] shall be consistent with drug product final specifications”.

The second principle is this regulation further requires that in-process specifications “shall be derived determined by the application of suitable statistical procedures were appropriate”. The cGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations (§ 211.42). Equipment must be of appropriate design, adequate size, and suitable located to facilitate operations for its intended use (§ 211.63). Automated, mechanical and electronic equipment must be calibrated, inspected, or checked according to the written program designed to assure proper performance (§ 211.68).

In summary, the cGMP regulations require that manufacturing processes be designed and controlled to assure that in-process material and finished product meet predetermined quality requirements and do so consistently and reliability throughout product lifecycle.

Approach to Process Validation⁵

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

The various stages along with their purpose and activities is summarized in Table No 1.

Table 1: Summary of various stages in process validation.⁸

| Stage | Purpose | Typical Activities |
|--------------------------------|---|---|
| Process Design | To define the commercial process on knowledge gained through development and scale up activities. The outcome is the design of a process suitable for routine manufacture that will consistently deliver product that meets its critical quality attributes. | <ul style="list-style-type: none"> ✓ A combination of product and process design (Quality by Design). ✓ Product development activities. ✓ Experiments to determine process parameters, variability and necessary controls. ✓ Risk assessments. ✓ Other activities required to define the commercial process. ✓ Design of Experiment testing |
| Process Qualification | To confirm the process design as capable of reproducible commercial manufacturing. | <ul style="list-style-type: none"> ✓ Facility design. ✓ Equipment & utilities qualification. ✓ Process Performance qualification (PPQ). ✓ Strong emphasis on the use of statistical analysis of process data to understand process consistency and performance. |
| Continued Process Verification | To provide ongoing assurance that the process remains in a state of control during routine production through quality procedures and continuous improvement initiatives. | <ul style="list-style-type: none"> ✓ Proceduralised data collection from every batch. ✓ Data trending and statistical analysis. ✓ Product review. ✓ Equipment and facility maintenance. ✓ Calibration. ✓ Management review and production staff feedback. ✓ Improvement initiatives through process experience. |

Process Validation Scheme

The following models (Figure1-9) may be useful in determining whether or not a process should be validated: By the help of these models, we can design and adopt a set of validation procedures to validate the different changes which are bound to occur or made in the routine production.

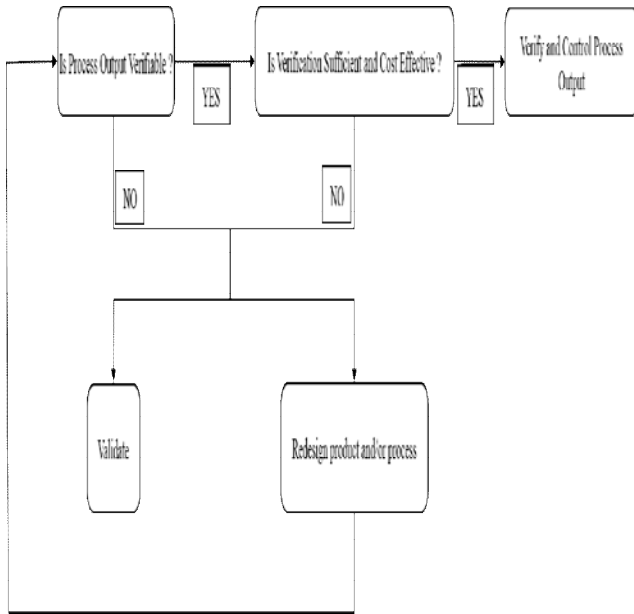


Figure 1: Process Validation Scheme.

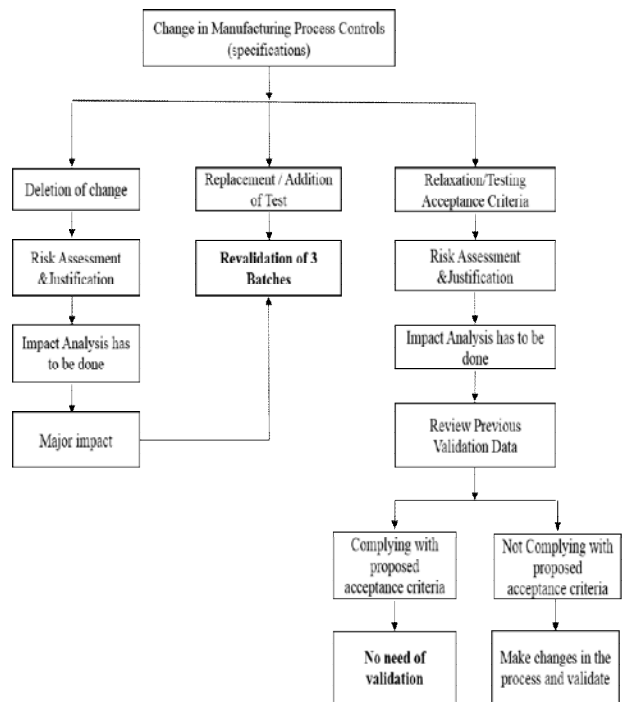


Figure 2: Process Validation Scheme for change in manufacturing process controls (specifications)

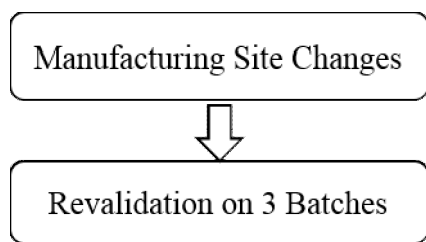


Figure 3: Process Validation Scheme for change in manufacturing site.

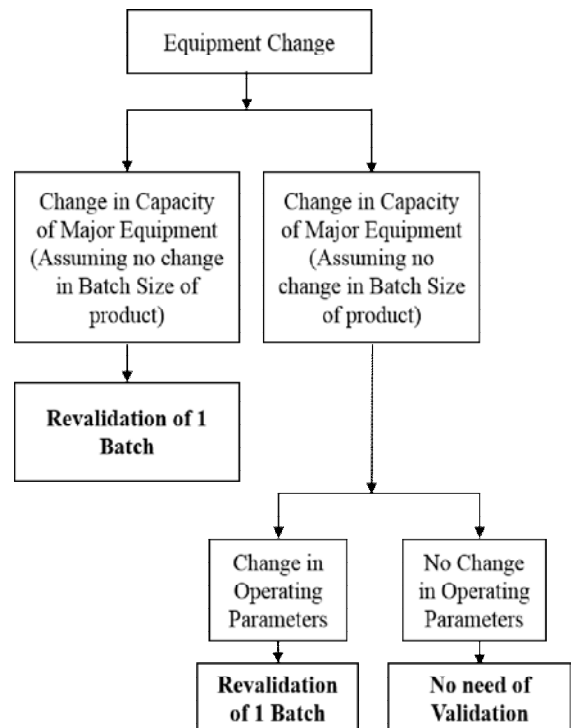


Figure 4: Process Validation Scheme for Equipment Change.

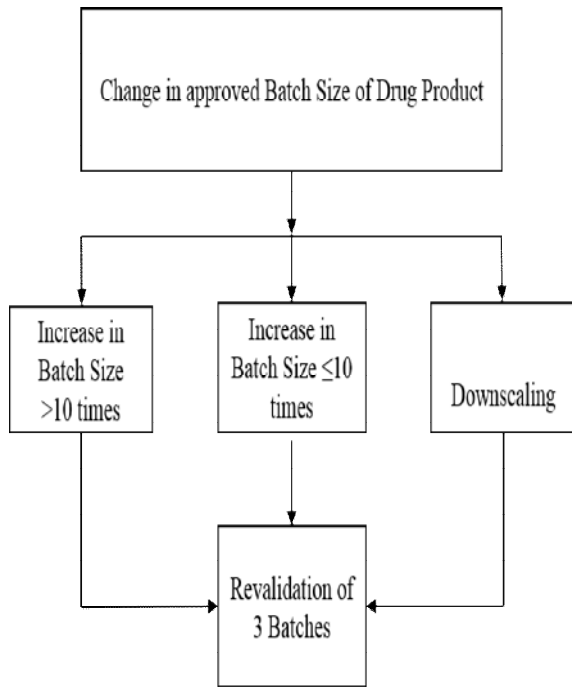


Figure 5: Process Validation Scheme for change in approved Batch size.

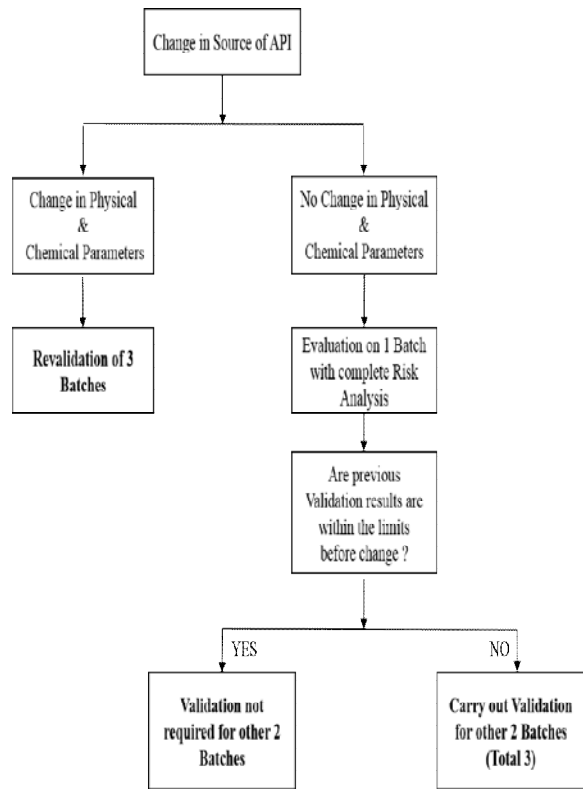


Figure 6: Process Validation Scheme for change in source of API.

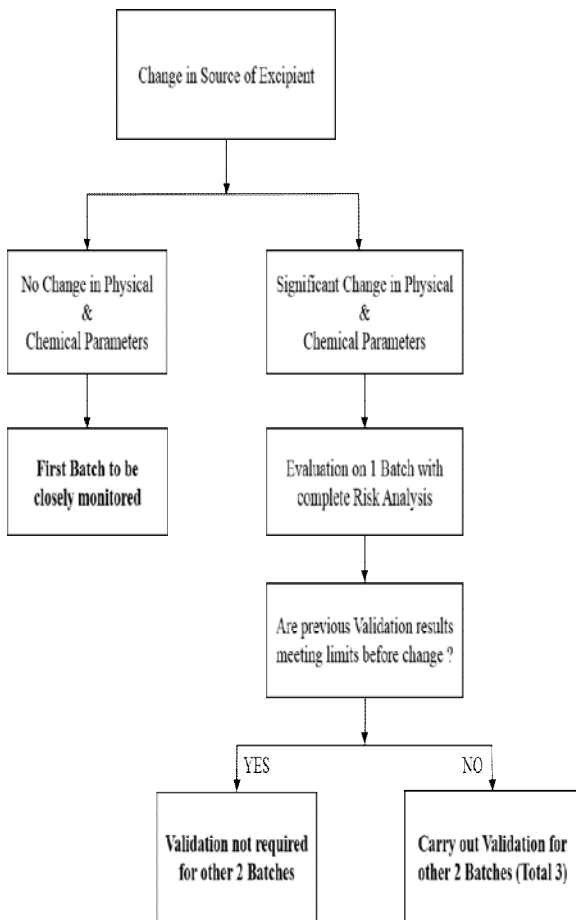


Figure 7: Process Validation Scheme for change in source of Excipient.

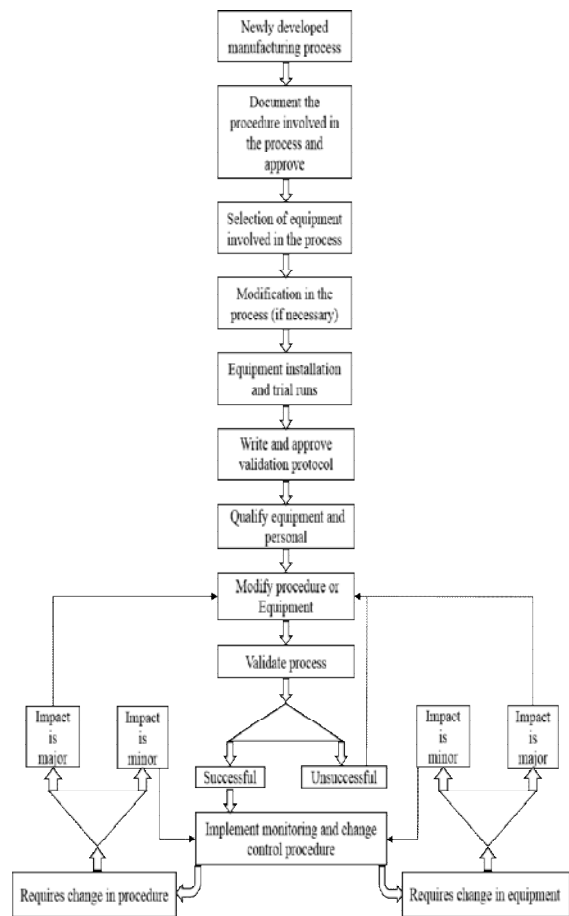


Figure 8: Validation of newly developed manufacturing process.

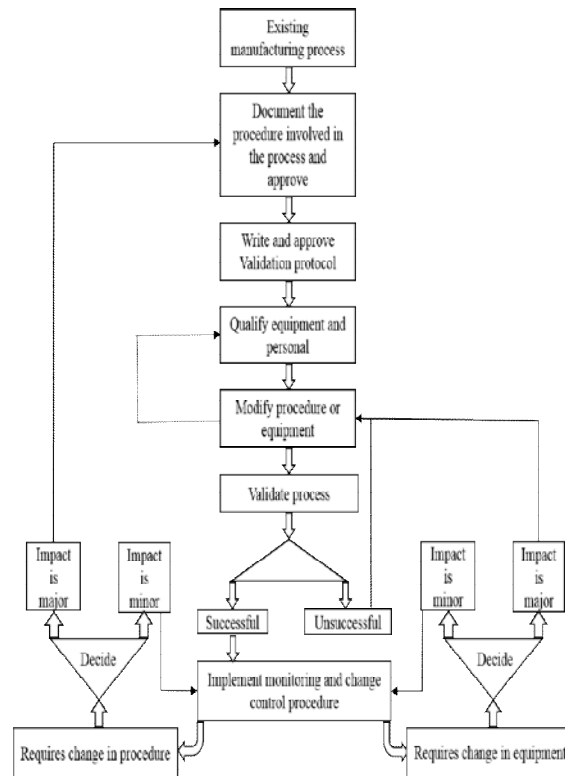


Figure 9: Validation of existing manufacturing process.

Process Description and Process Parameters^{2,10-12}

The following process parameters (Table No2) are recommended to be controlled or monitored as part of the process validation of tablets.

Table 2: Parameters to be monitored during process validation of tablets.

| Process Flow/Steps | Process parameters |
|---|--|
| Raw Material Sieving | Sieve / Mesh size |
| Premix | Mixing time, Speed, Load size |
| Dry milling(Particle sizing) | Screen size, Milling speed, Feed rate |
| Mixing or Blending | Mixing or Blending technique, speed & time and Homogeneity. |
| Wet Granulation | Granulating solvent/agent, Concentration & Addition of granulating solvent/agent, Mixing time and Granulation end point. |
| Wet Milling | Equipment size and capacity, Screen size, Mill speed and Feed rate. |
| Drying | Inlet/outlet temperature, Airflow, Moisture uniformity, Moisture content and Equipment capacity. |
| Dry Milling | Mill size and capacity, Screen size, Mill speed and Feed rate. |
| Tableting / Tablet compression | Tooling, Compression speed, Compression / ejection force and IPQC tests. |
| Coating | Equipment type, Coater load, Pan speed, Spray guns, Spray rate, Tablet flow, Inlet / outlet temperature and air flow, Coating solution, Coating weight and Residual solvent level. |
| Printing on product | Printing speed (tablets/hour) and Temperature. |
| Primary packing | Machine settings, Machine speed and Feeding speed. |
| Environment monitoring during the manufacturing process | Temperature and Relative humidity. |
| In-process quality control tests | Moisture content of dried granules, Granule particle size distribution, Blend uniformity, Weight variation, Tablet hardness, Tablet thickness, Disintegration, Dissolution and Impurity profile. |
| Finished product quality control tests | Appearance, Assay, Content uniformity, Tablet hardness, Tablet thickness, Tablet friability, Disintegration, Dissolution and Impurity profile. |
| Key test parameters or Major process variables | Mixing time and speed during blending and granulation, Solvent addition rate during granulation, Time, temperature and airflow pattern during drying and coating, Milling speed in mills and Machine speed and compression force during compression. |

CONCLUSION

The cGMP regulation requires that the manufacturing process should be designed and controlled to assure that in-process materials and finished product should meet the predetermined specifications and quality attributes. Process validation of tablets involves a series of activities taking place around the lifecycle of the product.

The information obtained during the preformulation stage is essential and forms the basis to identify, prioritize and control process parameters to be closely monitored in the course of process validation schedule to ensure the quality of the final product.

In this review the process validation schemes for any changes during the manufacture of tablets is explained. Hence it can be concluded that process validation of tablets in industries encompasses the manufacturing activities and changes.

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