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Review Article

Validation of Solid Dosage form (Tablets): A Review

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ABSTRACT

Validation is a establishing the documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. To further enhance the effectiveness and safety of the drug product after approval, many regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation and process controls are important in spite of the problems that may be encountered. This review provides an overview of pharmaceutical validation and process controls in formulation of tablet dosage form. There are generally eight major areas that included in process validation of tablets like, biobatch relationship, raw materials, manufacturing procedures and equipment, granulation/mix analysis, in-process controls, test results with validated methods, investigations/product failures and site review. Thus, validation concept can be applied to all the steps involving in tablet formulation.

Keywords: Validation, Process validation of tablets, Uses of validation, Validation protocol

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INTRODUCTION

Process validation is a requirement of the Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals, 21 CFR Parts 210 and 211 and therefore, is applicable to the manufacture of pharmaceuticals. Several firms have asked FDA for specific guidance on what FDA expects firms to do to assure compliance with the requirements for process validation. FDA recognizes that, because of the great variety of drug products, processes and manufacturing facilities, it is not possible to state in one document all of the specific validation elements that are applicable [1]. Several broad concepts, however, have general applicability, which manufacturers can use successfully as a guide in validating a manufacturing process. The Quality System (QS) regulation defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications [820.3(z) (1)]. The requirement for process validation appears in section 820.75 of the Quality System (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goals are met.

BASIC PRINCIPLES

The basic principles for validation may be stated as follows [2]:

- Establish that the process equipment has the capability of operating within required parameters;
- Demonstrate that controlling, monitoring, and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment;
- Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operated within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and
- Monitor the validated process during routine operation. As needed, requalify and recertify the equipment.

DEFINITION OF PROCESS VALIDATION

Process validation is establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics [3].

SIGNIFICANCE OF VALIDATION

- In general, validation is the process of checking if something satisfies a certain criterion.
- Validation implies one is able to document that a solution or process is correct or is suited for its intended use [4].
- In a quality management system, validation usually relates to confirmation that the needs of an external customer or user of a product, service, or system are met.
- Validation can mean to declare or make legally valid or to prove valid or confirm the validity of data, information, or processes.
- In computer terminology, validation refers to the process of data validation, controlling that data inserted into an application satisfies pre determined formats or complies with stated length and character requirements and other defined input criteria.
- In psychology and human communication, validation is the reciprocated communication of respect which communicates that the other's opinions are acknowledged, respected, heard, and (regardless whether or not the listener actually agrees with the content), they are being treated with genuine respect as a legitimate expression of their feelings, rather than marginalized or dismissed.
- In the medical device, pharmaceutical and biotechnology manufacturing industries, validation refers to establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes.
- In finance, validation is a process part of the "trade life-cycle."
- Validation is important because it disallows data that can not possibly be either true or real to be entered into a database or computer system.
- Validation against an incomplete or insufficient set of criteria can lead to a state of "validated" where "validated" does not confer the confidence that the term intends. Thus validation of the validation criteria is an important aspect that is often overlooked.

VALIDATION PROTOCOL

A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

It is important that the manufacturer prepare a written validation protocol, which specifies the procedures (and tests) to be conducted and the data to be collected. The purpose for which data are collected must be clear; the data must reflect facts and be collected carefully and accurately. The protocol should specify a sufficient number of replicate process runs to demonstrate reproducibility and provide an accurate measure of variability among successive runs. The test conditions for these runs should encompass upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure compared to ideal conditions; such conditions have become widely known as "worst case" conditions. (They are sometimes called "most appropriate challenge" conditions.) Validation documentation should include evidence of the suitability of materials and the performance and reliability of equipment and systems. The validation protocol should contain the following information:

1. General information
2. Objective
3. Background/ Prevalidation Activities
4. List of equipment and their qualification status
5. Facilities qualification
6. Process flow chart
7. Manufacturing procedure narrative
8. List of critical processing parameters and critical excipients
9. Sampling, tests and specifications
10. Acceptance criteria

REVALIDATION

There should be a quality assurance system in place, which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes, which could impact on product effectiveness or product characteristics, and whenever there are changes in product characteristics. Furthermore, when a change is made in raw material supplier, the manufacturer should consider subtle, potentially adverse differences in the raw material characteristics. A determination of adverse differences in raw material indicates a need to revalidate the process. One way of detecting the kind of changes that should initiate revalidation is the use of tests and methods of analysis, which are capable of measuring characteristics, which may vary. Such tests and methods usually yield specific results, which go beyond the mere pass/fail basis, thereby detecting variations within product and process specifications and allowing determination of whether a process is slipping out of control. The extent of revalidation will depend upon the nature of the changes and how they impact upon different aspects of production that had previously been validated. It may not be necessary to revalidate a process from scratch merely because a given circumstance has changed. However, it is important to carefully assess the nature of

the change to determine potential ripple effects and what needs to be considered as part of revalidation.

ELEMENTS OF PROCESS VALIDATION [6,7]

A. PROSPECTIVE VALIDATION

Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product validation -product's characteristics. Prospective validation includes those considerations that should be made before an entirely new product is introduced by a firm or when there is a change in the manufacturing process which may affect the product's characteristics, such as uniformity and identity. The following are considered as key elements of prospective validation.

1. Equipment and Process

The equipment and process (es) should be designed and/or selected so that product specifications are consistently achieved. This should be done with the participation of all appropriate groups that are concerned with assuring a quality product, e.g., engineering design, production operations, and quality assurance personnel.

a. Equipment: Installation Qualification

Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. After process equipment is designed or selected, it should be evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process. This phase of validation includes examination of equipment design; determination of calibration, maintenance, and adjustment requirements; and identifying critical equipment features that could affect the process and product. Tests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results. All acceptance criteria must be met during the test or challenge.

b. Process: Performance Qualification

The purpose of performance qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. Each process should be defined and described with sufficient specificity so that employees understand what is required. Each specific manufacturing process should be appropriately qualified and validated.

c. Product: Performance Qualification

Before reaching the conclusion that a process has been successfully validated, it is necessary to demonstrate that the specified process has not adversely affected the finished product. Where possible, product performance qualification testing should include performance testing under conditions that simulate actual use. Product performance qualification testing should be conducted using product manufactured from the same type of production equipment, methods and procedures that will be used for routine production. After actual production units have successfully passed product performance qualification, a formal technical review should be conducted and should include: comparison of the approved product specifications and the actual qualified product, determination of the validity of test methods used to determine compliance with the approved specifications and determination of the adequacy of the specification change control program.

2. SYSTEM TO ASSURE TIMELY REVALIDATION

There should be a quality assurance system in place, which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes, which could impact on product effectiveness or product characteristics, and whenever there are changes in product characteristics. Furthermore, when a change is made in raw material supplier, the manufacturer should consider subtle, potentially adverse differences in the raw material characteristics. A determination of adverse differences in raw material indicates a need to revalidate the process.

The quality assurance procedures should establish the circumstances under which revalidation is required. These may be based upon equipment, process, and product performance observed during the initial validation challenge studies. It is desirable to designate individuals who have the responsibility to review product, process, and equipment and personnel changes to determine if and when revalidation is warranted.

3. DOCUMENTATION

It is essential that the validation program is documented and that the documentation is properly maintained. Approval and release of the process for use in routine manufacturing should be based upon a review of all the validation documentation, including data from the equipment qualification, process performance qualification, and product/package testing to ensure compatibility with the process. For routine production, it is important to adequately record process details (e.g., time, temperature, equipment used) and to record any changes, which have occurred. A maintenance log can be useful in performing failure investigations concerning a specific manufacturing lot. Validation data (along with specific test data) may also determine expected variance in product or equipment characteristics [8].

B. RETROSPECTIVE PROCESS VALIDATION

Retrospective Validation of a process for a product already in distribution based upon accumulated production, testing and control data. In some cases a product may have been on the market without sufficient premarket process validation. In these cases, it may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data on the product and records of the manufacturing procedures used.

Retrospective validation can also be useful to augment initial premarket prospective validation for new products or changed processes. In such cases, preliminary prospective validation should have been sufficient to warrant product marketing. As additional data is gathered on production lots, such data can be used to build confidence in the adequacy of the process. Conversely, such data may indicate a declining confidence in the process and a commensurate need for corrective changes. Test data may be useful only if the methods and results are adequately specific. As with prospective validation, it may be insufficient to assess the process solely on the basis of lot-by-lot conformance to specifications if test results are merely expressed in terms of pass/fail. Specific results, on the other hand, can be statistically analyzed and a determination can be made of what variance in data can be expected. It is important to maintain records, which describe the operating characteristics of the process, e.g., time, temperature, humidity, and equipment settings.

PARAMETERS REQUIRED TO BE CONSIDERED FOR VALIDATION OF AN ORAL SOLID DOSAGE FORM MANUFACTURING PROCESS (TABLETS)

There are at least eight major areas that must be included in process validation of tablets [9-11] i.e. biobatch relationship, raw materials, manufacturing procedures and equipment, granulation/mix analysis, in-process controls, test results with validated methods, investigations/product failures and site review.

RAW MATERIALS

Physical characteristics of raw materials can vary among manufacturers of drug substances and, on occasion, have varied from lot to lot from the same manufacturer. Upon examination of retain samples of the lots of raw material, obvious physical differences between the two lots may be observed. Inspections should cover the firm's data for the establishment of their physical specifications for drug substances. If the firm has no specification, or a very vague specification, they should be able to provide data to demonstrate that dissolution profiles and content uniformity will be satisfactory over a wide range of particle sizes. For example, a manufacturer may establish a specification of 90% of the particles must be less than 300 microns. For validation of this process, one would expect the use of micronized as well as material with particles close to 300 microns in size.

MANUFACTURING PROCEDURES AND EQUIPMENT

Regardless of the nature of the specificity of the manufacturing directions contained in the application, a detailed master formula with specific manufacturing directions and specifications must have been developed before any validation protocol is prepared and before the validation process begins. The basic premise of validation of a process is that a detailed process already exists which hopefully will be shown to perform consistently and produces products in compliance with predetermined specifications. Therefore, detailed manufacturing directions, specifying equipment and operating parameters must be specified in the master formula. The importance of specific written directions and specifications cannot be overemphasized. For example, problem areas may include: the failure to specify the amount of granulating solution, resulting in over wetting and dissolution failures of aged batches, the failure to specify the encapsulation machine and operating parameters, such as dosing discs, resulting in weight variation failures and the failure to specify the compression machine(s) and operating parameters, resulting in content uniformity failures.

The following is a brief description of some issues associated with equipment:

a. Blenders

Many solid oral dosage forms are made by direct compression. There are generally two types of mixers - low energy and high energy. The low energy mixers represent the classical type of slow mixers, such as ribbon blenders, tumblers, and planetary pony pan. The high energy mixers include some basic features of the low energy mixer but also contain some type of high-speed blade, commonly termed an intensifier bar or chopper. The usefulness of pony pan type mixers is limited to wet granulating. With this type of mixer, there is good horizontal (side to side) blending. In the ribbon blender, powder is mixed both horizontally and vertically. Loading operations can be dusty. Common mixers of tumbler blender type include the twin-shell and double cone. These mixers exert a gentle mixing action. Because of this mild action, lumps of powder will not be broken up and mixed. High Shear (high energy) mixers include GRAL, Diosna and Lodige or Littleford. These mixers are highly efficient and ideally suited for wet granulations. End point of wet granulations can be determined by a measurement on a gauge of the work needed to agitate the blend. For wet granulations, it is important to control the rate and amount of addition of the solvent. Because of their efficiency, drug substance may partially dissolve and recrystallize upon drying as a different physical form. Different variable parameters used in milling operations are screen size, milling speed and feed rate whereas the responses are particle size distribution/shape and loose/ tapped densities. The different variable parameters used in powder blending are blender time, speed and intensifier bar whereas the responses are content uniformity, assay, particle size distribution and powder flow. Whereas in lubrication the variables are blender speed, time and method of addition of lubricant and the different responses are particle size distribution, loose/ tapped densities, and tabletting characteristics like friability and hardness.

b) Dryers

There are two basic types of dryers i.e. oven dryer where the wet granulation is spread on trays and dried in an oven and fluid bed dryer in which the wet granulation is "fluidized" or suspended in air. Generally, the fluid bed dryer yields a more uniform granulation with spherical particles. However, this may result in compression problems that may require additional compression force. It is not unusual to see manufacturers change from an oven dryer to the fluid bed dryer. Other issues of concern with drying include moisture uniformity and cross contamination. Tray dryers present more moisture

uniformity problems than fluid bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to assure moisture uniformity in granulations at the end point of drying. With respect to fluid bed dryers, moisture problems can occur if the granulation is not completely fluidized. Different fixed parameters used in fluid bed drying are bowl charge, porosity of filter bags, bowl sieve; variable parameters inlet exhaust air temperature, product temperature, drying time, air volume, humidity of incoming air, humidity of exhaust air; and different responses are particle size distribution, densities, loss on drying, assay.

c) Tablet compression Equipment

Another important variable in the manufacturing process is the tablet press. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and requires a uniform granulation to function correctly. Different tablet compression equipment can cause dose uniformity, weight uniformity and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. Speed of the machine can affect fill of the die and tablet weight. Therefore, as previously discussed, it is important to have specific operating directions. Different variable parameters used in tablet compression machine are speed of press, precompression, compression force, feeder speed whereas the different responses are appearance, weight variation, hardness/ friability, thickness, moisture content, distribution/ dissolution and assay/ dose uniformity.

d) Coating Equipment

Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate and temperature can be controlled by some of the more highly automated operations. However, many sugar coated, enteric coated and delayed release products exist where some portions of the coating process are not highly soluble and are performed manually. Generally, the shellac undercoat used for sugar-coated tablets has presented disintegration/dissolution problems, particularly in aged samples. There have been many occasions when the coating process was not validated. The number of applications of coats, volume of coating solution in a specific application, and temperature of the solution during application is all parameters that need to be addressed. For example, the temperatures of application and even heat during drying have been found to cause dissolution failures in aged tablets. Another problem associated with the coating process concerns the heat applied to products that are sensitive to heat. For example, it has been shown that estrogen tablets are heat sensitive and have exhibited stability problems. Thus, it is important to control this phase of the process. Different variable parameters used in tablet coating process are pan load, inlet/exhaust temperatures, inlet/exhaust humidities, pan speed, spray nozzle size, atomizing pressure, spray rate and angle, tablet core characteristics and gun to bed distance whereas the different responses are percent weight gain, thickness, elegance, dissolution, residual solvent and degradation level.

GRANULATION/MIX ANALYSIS

A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender which have the greatest potential to be non-uniform can be sampled. This is particularly true of the ribbon type blender and planetary or pony type mixers. In some cases, such as for large or tumbler type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle and bottom of each drum should be collected. In most cases sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis. Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit should be sampled in order to test for uniformity. Many industrial pharmacy and engineering texts confirm this approach. Large granulation sample sizes, such as one ounce will provide little information with respect to uniformity. Generally, further mixing after sampling and prior to analysis occurs which yields misleading results. The acceptance criteria for granulation dose uniformity testing needs to be evaluated. Although many firms evaluate dose uniformity using the compendial dose uniformity specifications (85-115% with an RSD of 6 to 7.8), such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases compendia assay limits for the finished product (90 to 110% of label claim) are broad enough for this purpose, and most firms should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific USP or filed criteria for assay should be used. This key issue needs to be examined during the inspection. Different fixed parameters used in tablet granulation are equipment, and batch size; variable parameters are mixing speed, and amount of granulation fluid fed rate granulation time load; responses are drug distribution, water / solvent content, appearance(size), power consumption.

IN-PROCESS TESTING

In-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency throughout these operations. For tablets, individual tablet weights, moisture, hardness (compression

force) and disintegration are performed. For capsules, individual weights and moisture are performed. In many of the validation reports reviewed, manufacturers have neglected to supply individual (not composite) dosage unit weights performed throughout compression/encapsulation. This is particularly important for capsule products which may exhibit weight variation problems. If not part of validation reports, the individual dosage unit weights should be reviewed. Since hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate both equivalency (comparability) and consistency.

TEST RESULTS

Finished product testing, particularly assay, content uniformity and dissolution, should be reviewed. With regard to dissolution, it is important to review dissolution profiles. Validation batches with dissolution profiles not comparable to biobatches indicate non-equivalency of the manufacturing process. Depending on the discriminating nature of the dissolution test, it may also indicate lack of equivalence of the dosage forms made during validation with the biobatch. In the review of dissolution test results, it is important to eventually see results very close to 100% dissolution. In some cases, manufacturers will profile the dissolution results only to the specification. However, if lower, but still acceptable results are obtained (such as 85%), it is important to continue the test. This can be performed by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.

INVESTIGATIONS/PRODUCT FAILURES

In any process validation exercise, a basic objective is to prove that a process is satisfactory. Unfortunately, some processes are unsatisfactory and may sometimes yield unacceptable results. It is important, therefore, that when the final validation report is reviewed, all results, including failing results, be discussed and evaluated. For example, review of a manufacturing process showed that one of every eight batches manufactured failed content uniformity. Members of the company recognized that the process was unsatisfactory and not validated, but failed to draw this conclusion in the written validation report. When reviewing a validation report, the basis for concluding that a process is satisfactory, particularly those with failing results should be evaluated.

SITE REVIEW

A major aspect and possibly the most critical phase of the inspection of process validation is the review of data at the manufacturer. Manufacturers have presented validation reports, which appeared to be very complete, however, when data was actually reviewed, failing batches were omitted without justification. Additionally, review the raw data, including analytical raw data, for accuracy. Only through on-site audit or review of data could such situations be identified. Thus, even though a pre-approval inspection is performed, a post-approval inspection providing for a review of validation data is warranted, particularly in those cases in which deficiencies in validation data have been identified.

CONCLUSION

Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of repeatedly and reliably producing a finished product of the required quality. It would normally be expected that process validation be completed prior to the release of the finished product for sale (prospective validation). Where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes, which have been in use for some time without any significant changes, may also be validated according to an approved protocol (retrospective validation). In tablet production, there are many unit operations which have to be follow successfully for their production. Thus, at every step, pharmaceutical validation and process control are necessary to ensure that the tablet will meet/set pharmaceutical standards for identity, strength, quality, purity, stability, evaluation safety and efficacy. In general, pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured

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