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CURRENT CHALLENGES IN PROCESS VALIDATIONS

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ABSTRACT

From the study, it can be stated that current challenges in process validation is a major requirement of cGMP regulation for finished pharmaceutical products. It is a key element in assuring that the quality goals are met. Successfully validating a process may reduce the dependence upon intensive in process and finished product testing. Finally, it can be concluded that Process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product.

KEYWORDS: current challenges in process validation, pharmaceutical product.

1. INTRODUCTION

Validation is a concept that has evolved in united states in 1978.The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control, Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP.[1]

The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant. This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished product inspection or testing each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. Process controls include raw materials inspection, inprocess controls and targets for final product. The purpose is to monitor the online and off-line performance of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance.[2 & 3]

Validation mainly based on, FDA regulations describing current good manufacturing practice (cGMP) 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.[3]

1.1. HISTORY OF VALIDATION

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals (Agalloco 1995). It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated process of pharmaceutical. U.S.F.D.A. was the pioneer in advocating the concept of process validation, but till 29th September 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. no cGMP regulations talked anything about process validation.[4]

A. Definitions

European commission 1991 –Validation-"Act of proving, in accordance of GMPs that Any…" process actually leads to expected results. 2000 -"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".

US FDA Definition "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."

ICH Definition "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."

WHO Definition "The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result".[5]

Process Validation

Process validation provides the flexibility and constraints in the production process controls in the achievement of desirable qualities in the drug product while preventing undesirable attributes (Figure1).

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.[6]

Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and revaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process those results in products with the desired quality attributes.

Manufacturers should

•Understand the sources of variation
•Detect the presence and degree of variation
•Understand the impact of variation on the process and ultimately on product attributes
•Control the variation in a manner commensurate with the risk it represents to the process and product.[7]

OBJECTIVE OF PROCESS VALIDATION

- To reduce variation between various batches.
- To provide a high degree of assurance of quality of the product.
- To decrease the risk of defect costs and regulatory noncompliance.
- To ensure the consistency of the manufacturing operation and reproducibility of the process.
- To demonstrate the robustness of the process.
- A fully validated process may require less in-process controls and end product testing.
- To ensure the existence of all necessary quality assurance system within organization.

REASON FOR PROCESS VALIDATION

The possible reason of performing process validation may include.

- New product or existing products as per SUPAC changes.
- Change in site of manufacturing.
- Change in batch size.
- Change in equipment.
- Change in process existing products.
- Change in composition or components.
- Change in the critical control parameters.
- Change in vendor of API or critical excipient.
- Change in specification on input material.
- Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
- Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

ADVANTAGES OF PROCESS VALIDATION

1. It is simple process and moisture sensitive and heat sensitive products can also be processed.
2. Expanded real time monitoring and adjustment of process.
3. Decreases the risk of preventing problems and thus assure the smooth running of the process.
4. Enhanced ability to statistically evaluate process performance and product variables e.g. individuals; mean; range; control limits.
5. Enhanced data and evaluation capabilities and increased confidence about process Reproducibility and product quality.
6. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
7. Enhanced reporting capability.
8. Assurance of quality.
9. Process optimization.
10. Reduction of quality cost.
11. Minimal batch failures, improved efficiently and productivity.[8, 9 &10]

1.2. TYPES OF VALIDATION

A). Prospective validation

The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

B). Concurrent validation

It is a process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch. Concurrent Validation means establishing documented evidence a process does what it is supposed to based on data generated during actual implementation of the process. Concurrent validation may be the practical approach under certain circumstances. It is important in these cases when the systems and equipment to be used have been fully validated previously.

C). Retrospective validation

Conducted fir a product already being marked, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which is now to be validated to confirm to the requirements of division 2, Part C of the Regulation to be Food and Drugs Act. Retrospective Validation is only acceptable for well established detailed processes and will be Inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility.

D). Revalidation

Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. Re-validation becomes necessary in certain situations.[11]

1.3. 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 attributes. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages.

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. .A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process those results in products with the desired quality attributes. Manufacturers should understand the sources of variation off,

- Detect the presence and degree of variation
- Understand the impact of variation on the process
- Ultimately on product attributes. Control the variation in a manner commensurate
- With the risk it represents to the process and product.

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product. Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.[12]

1.4. Basic principle for process validation

The basic principle for validation may be stated as follows.

A. Installation Qualification (IQ)
B. Operational Qualification (OQ)
C. Performance Qualification (PQ)

1.5. Validation team

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies. The working party would usually include the following staff members such as;

- Head of quality assurance.
- Head of engineering.
- Validation manager.
- Production manager.
- Specialist validation discipline: all areas.

- The validation team must be Prepare the site validation master plan with the specific requirements as per the company policy.
- Meet regularly, In accordance with a defined schedule, to discuss the progress and compliance with the validation plan and schedule.
- Determine the systems / equipment to be qualified / validated and the extent of validation to be carried out.
- Determine the frequency of validation Prepare and evaluate the suitability of the protocols.
- Verify the adequacy of the tests used for proving that the objectives are achieved.

Complied reports should be checked and approved by validation team member's .Maintain records of validation studies and inform to the Corporate Quality Assurance of progress in terms of validation plan and schedule.[17]

1.6. Validation master plan:

The validation master plan should provide an overview of the entire validation operation, it organizational structure, its content and planning. The main elements of it being the list/inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as revalidation.

The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports.

The format and content should include

Introduction: validation policy, scope, location and schedule.
Organizational structure: personnel responsibilities.
Plant/process/product description: rational for inclusions or exclusions and extent of validation .
Specific process considerations that are critical and those requiring extra attention.
Key acceptance criteria.
Documentation format.
Reference to the required SOPs.
Time plans of each validation project and sub-project.
List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.
Re-validation activities, actual status and future planning.[18]

1.7. The validation report

A written report should be available after completion of the validation, if found acceptable it should be approved and authorized.
The report should include at least the following Title and objective of study.
Reference to protocol.
Details of material.
Equipment.
Programes and cycles used.
Details of procedures and test methods.
Result
Recommendations on the limit and criteria to be applied on future basis.[19]

1.8. Importance of process validation

Assurance of Quality Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the capabilities of that process without validated and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for variety reasons, among which are.
1. Very limited sample size.
2. The limited number of tests performed on a sample. For example, it is impractical to test for all potential impurities or contaminants.
3. The limited sensitivity of the test.

Process Optimization The optimization of a process for maximum efficiency, while maintaining quality standards, is a consequence of validation. Literal meaning of word to optimize is "To make as effective, perfect or useful as possible".

The optimization of the facility, equipment, systems, and processes results in a product that meets quality requirements at the lowest cost. Reduction of quality costs Quality costs are divided in to four categories. They are.
a) Preventive costs.
b) Appraisal costs.
c) Internal failure costs.
d) External failure costs. e.g. of internal failure costs: Any validated and controlled process will result in fewer internal failures like;
Fewer rejects
Reworks
Re-tests
Re-inspection.[20]

1.9. APPLICATION OF PROCESS VALIDATION

Validation is basically good business practice. It helps in following.

1. Regulatory Requirement

Validation is regulatory requirement for the cGMPs and USFDA all over the world. The cGMP basically serve as guidelines but do not provide step-by-step directions on how to achieve them. However, the validation master plan and associated SPOs exactly responsibilities: who, when, where, and how much is sufficient to demonstrate. Improve employee awareness of processes.

2. Quality Assurance
Validation provides confidence in the quality of product of products manufactured as the over quality of a particular process cannot be established due to the limited sample size. Validation leads to less troubleshooting with routine production. As a result it reduces the number of customer complaints and drug recalls.

3. Cost Cutting Tool
Validation is a tool for cutting the cost; it is comprised of preventive, appraisal, internal failure external failure. The preventive cost includes quality planning, vendor approval, training, documentation and preventive maintenance, calibration and sanitation cost. The Appraisal cost include inspection of raw material In-process material, finished product and stability testing, the internal failure cost include re-inspection, retesting, rework, and rejection and external failure cost include recall, complaints and return due to quality issue. Validation leads to the optimization of processes and results in minimization of those expenses. Reduction in rejections and reworks. Reduction in utility cost. Avoidance of capital expenditures.

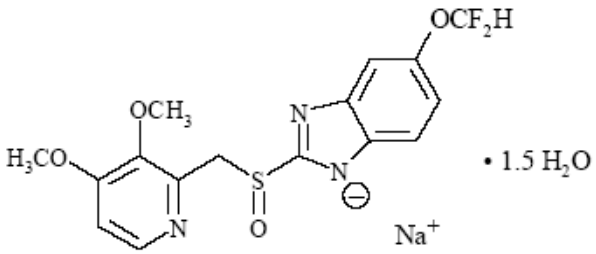
4. Reproducibility
The product obtained from process validation shows reproducibility in quality, purity, strength and also shows consistency in results.
5. Easier scale-up from development work.
6. Easier maintenance of equipment.
7. Improve employee awareness of processes.
8. More rapid automation.[21 & 22]

RESULTS AND DISCUSSION

5.1. Process Validation of Pantoprazole Tablets

Description
Pantoprazole sodium Tablets are substituted, Benzimidazole, sodium 5 (difluoromethoxy)-2-[[(3, 4-dimethoxy-2- pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole Sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is C16H14F2N3NaO4S x 1.5 H2O, with a molecular weight of 432.4.[45,46&48]

The structural formula is.



Pantoprazole

Label Claim
Each enteric coated tablet contains;
Pantoprazole sodium sesquihydrate equivalent to
Pantoprazole 40 mg.

Manufacturing Formula

Name of the material	Function
Pantoprazole sodium sesquihydrate	Active pharmaceutical ingredient (API)
Mannitol	Diluent
Anhydrous sodium carbonate	Stabilizer
Hypromellose	Binder
Crospovidone	Disintegrate
Calcium stearate	Lubricant
Hypromellose	Film former
Povidone	Plasticizer
Titanium dioxide	Anti-taking agent
Propylene glycol	Opacifier
Iso propyl alcohol	Vehicle
Methacrylic acid copolymer	Film former
Sodium hydroxide	Neutralizing agent
Macrogols	Plasticizer
Purified talc	Glident
Titanium dioxide	Opaquent/Colourant

Process Flow Chart

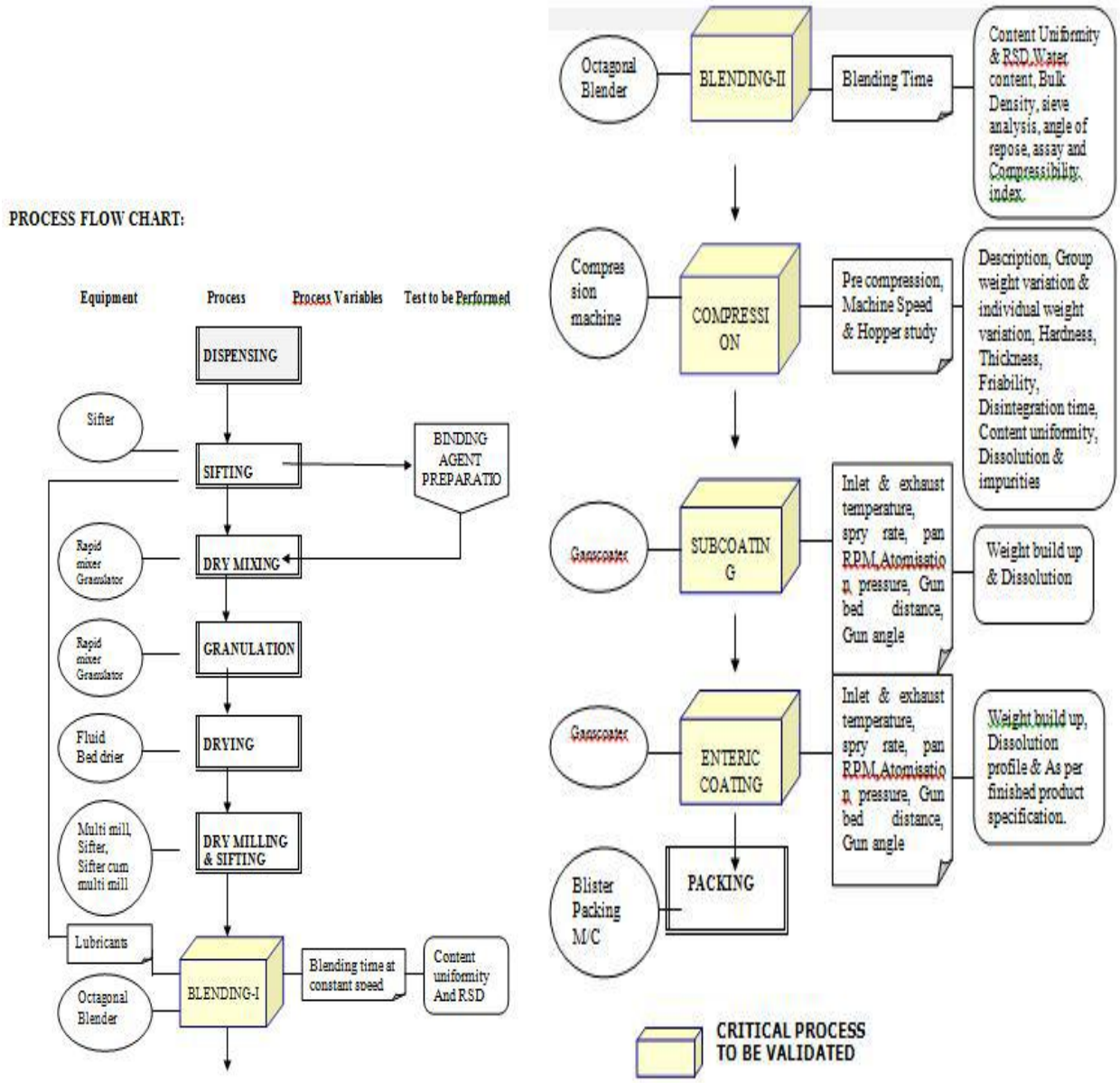


Figure 7: Process flow chart of Pantoprazole Tablets.

5.2. Description of Work:

Pantoprazole 40 tablets are validated to improve the dissolution properties. It is proposed to reducethe quantity of Calcium stearate from 3.20mg per tablet to 1.60mg per tablet and to compensate the quantity with Crospovidone is increased from 10.0mg to 11.60 mg per tablet .Since this change is at blending stage, subsequent impact to be studied further stages also, So the process needs to be validated for blending, compression and coating stages those are mentioned in above flow chart (Figure 7).

Dry mixing, granulation, drying stages remains same. Most widely used lubricants are of the hydrophobic category. Hydrophobic lubricants are generally good lubricants and are usually effective at relatively low concentrations. Many also have both anti- adherent and glidant properties. For these reasons, hydrophobic lubricants are used much more frequently than hydrophilic compounds. Calcium stearates have long been recognized in the art of pharmaceutical compounding as lubricants and are probably the most common pharmaceutical lubricants in use at the present time. These substances, however, in spite of their wide acceptance in the pharmaceutical arts as lubricants have certain disadvantages.

Determining the level of lubricants to useand the manner in which they are incorporated into a batch is critical. If concentrations are **too low**, or distribution and mixing times are inadequate, problems can arise.
Some examples are as follows:

- Punch filming
- Picking
- Sticking
- Capping
- Binding in the die cavity.

If concentrations are **too high**, or distribution and mixing times are too great, potential problems include:

- Decrease in tablet hardness
- Inability to compress into tablets
- Increase in tablet disintegration times (DTs)
- Decrease in rate of dissolution

The primary disadvantage to the use of calcium stearate as pharmaceutical lubricants lies in the fact that they are extremely hydrophobic. This hydrophobicity hinders dissolution and disintegration time of solid dosage forms containing magnesium and calcium stearates. Another factor which acts to hinder dissolution and disintegration time of solid dosage forms containing magnesium or calcium stearate is their electrostatic attraction with therapeutically active substances and other excipients [36&37].

Challenges and Its Process Parameters for Validation

Blending

This step involves mixing of granules with other blending material. The purpose of blending is to get a uniform distribution of pantoprazole sodium sesquihydrate.This is followed by mixing of the blend with calcium stearate (Lubrication to get good flow and anti-adhesion property of the blend.

The proper blending shall be established by checking content uniformity of drug at all the time intervals mentioned in protocol. In addition to this following tests shall be carried out for information purpose. This shall be carried out on final time interval samples only.

A) Water content
B) Bulk density
C) Sieve analysis
D) Compressibility index
E) Content uniformity & RSD
F) Angle of Repose
G) Assay

Compression

This step involvesConversions of blended material into tablets as per specifications. Speed of machine, tablet thickness and hopper level are the major variables. So, following parameters are to be checked to establish the above-mentioned variables at regular intervals like,

A) Description
B) Weight variation (group and individual)
C) Hardness
D) Thickness
E) Friability
F) Disintegration time
G) Dissolution time
H) Content uniformity and
I) Impurities

Coating

The coating step involves the covering of tablet surface with a polymer film. The pan RPM, Inlet and Exhaust temperatures, Spray rate, gun distance and air pressure are critical process variables. These parameters affect the coating and final appearance of the tablets.[44&45]

Table No 7: Testing of physical parameters as mentioned in the below table.

S.No	Parameter	Standard	Number of Tablets to be taken from each side for testing
1	Description	White to off white coloured round uncoated biconvex tablet plain surface on both sides.	10 Tablets
2	Total Weight variation	3.1 g ± 2% (3.038 g-3.162 g)	20 Tablets
3	Individual Weight variation	155 mg ± 4% (148.8 mg -161.2 mg)	40 Tablets
4	Hardness	NLT 2.5 Kg/cm 2	6 Tablets
5	Thickness	3mm±0.2mm(2.80mm-3.20mm)	10 Tablets
6	Disintegration time	NMT 12min	6 Tablets
7	Friability	NMT 0.8 % w/w	20 Tablets

Table: 8: Acceptance criteria for critical in process

Stage	Process variables	Sampling frequencies	Testes to be Performed	Approximate sample size	Acceptance criteria
Blending	Blending time	18 and 20 min	uniformity of content and RSD	3X13 samples at each time interval between 153.4 mg to 460.2mg in butter paper	100±15% RSD NMT
		23min	uniformity of content and RSD	3X13 samples at each between 155mg to 465mg in butter paper	
			Bulk density, sieve analysis, compressibility index , angle of repose, water content, and assay	100g from the blender in poly bags	for information
compression	precompression studies at optimum speed	At lower and higher thickness	Dissolution	3X12 tablets	As per current finished product specifications
	At three different machine speeds	At different speeds	Description	40 Tablets	White to off white coloured round uncoated biconvex tablet plain surface on both sides.
	Hopper study at max speed	Full hopper approximately middle hopper and near end hopper	Individual Weight variation	40 Tablets	155 mg ± 4% (148.8 mg -161.2 mg)
			Hardness	6 Tablets	NLT 2.5 Kg/cm 2
			Thickness	10 Tablets	3mm±0.2mm(2.80mm - 3.20mm)
			Disintegration Time	6 Tablets	NMT 12min
			Friability	20 Tablets	NMT 0.8 % w/w
			Content Uniformity	3X12 tablets	100±15%RSD; NMT 6.0%

5.3. Current challenges in process validation

Changing the existing validation culture to meet the expectations of the new guidance may be the biggest challenge industry faces. The guidance requires companies to expand their current scope of validation by reaching further upstream into development and downstream into day-to-day manufacturing. Companies agree this expansion will foster better communication from the development groups through to manufacturing but are concerned that it also requires additional staffing. To better understand and meet this challenge, companies should create gap analyses of their current state of validation and compare it with the future state based on the new guideline. These gap analyses will better situate companies to create action plans for the new policies and procedures that may need to be put into place. The analyses will also assist in identifying any resource gaps and training needs [41&42].

There are four main challenges

1. Technical Transfer of older products
2. Knowledge Accumulation
3. Stage 3 Continued Process Verification
4. Statistical Sampling

1. Technical Transfer of older products

Companies have developed in depth Technical Transfer processes for new products

•Thoroughly investigate the new processes.

•What about older ones that have to move to make room for the new processes.

•Most companies have a single tech transfer process.

It is essential that activities and studies resulting in process understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant."

"Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall."

Difficulty comes from

−Development may not have been done well for older products

−Maintenance of the Knowledge Data base

−Interest in sending site giving information to receiving site

Development may not have been done well for older Products
−Redevelop the process at the receiving site
−In depth analysis of the existing process thorough documenting the process
−Having technical person from the receiving site "live" at the sending site and focus activities on learning about the process.

Maintenance of the Knowledge Data base
−Build it from
−Batch records
−Investigations
−Annual product reviews
−Begin developing as production continues
•Interest in sending site giving information to receiving site
−Utilize a team comprised of technical individuals from both sites
−Minimize "fear" at sending site.

2. Knowledge Accumulation
"Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enabling organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce."

Difficulty comes from
−Multisite/multinational companies
−Maintenance of the database
−Multiple contributors

Creation of a Centralized Repository
−Web based on intranet
−Must be searchable
−Must have common terminologies
•Keep it up to date
−Process engineers responsible for gathering data and adding to the database
−Include links to APRs
−Include links to investigations
•Allow for multiple contributors (different sites same products)
•Still a challenge

3. Stage 3 Continued process verification
"An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel."

"We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates."

Difficulty comes from:
−Deciding where to document the program
−Continued sampling at the PQ levels

Deciding where to document program
−Utilize current Annual Product Review program
−Enhanced Annual Product Review program
−More emphasis on equipment changes
−Review of sample result variability
−Ensure thorough statistical evaluation and not just of finished product release data.

Continued Sampling at Performance Qualification Levels
−Pre-plan the activity (protocol) before PQ/PV runs
−Allow for changes in the number of batches (more or less)
−Staff the lab
−Plan for longer release times
−"Revalidation" Activities
−Time driven – Revert to standard sampling with rationale
−Change driven – Same approach as for "new" process but may be less.

'4. Statistical Sampling
In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch. The increased level of scrutiny, testing, and sampling should continue through the process verification stage as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process. Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes."

Difficulty comes from
−What are the expectations – no guidance.
Establish was confidence level your company wants (greater the confidence (e.g. 95%) means more samples.
•Establish the number of batches (3?)
•Be wary of using statistical techniques from other industries that sample/test differently
•Enhance your knowledge at small scale
−Utilize "PAT" techniques
−Utilize indicator tests for a component
−Utilize other similar product information (ensure the rationale)

–"Previous credible experience with sufficiently similar products and processes can also be helpful."[39&40]

SUMMARY AND CONCLUSION

It can be stated that process validation is major requirement of cGMPs regulation for the process efficiency and sturdiness from the review validation data on pharmaceutical process validation and process control variables of tablets manufacturing processes in industry and it is the full-fledged quality attributing tool for the pharmaceutical industries. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing.

The multidisciplinary approach to validation of solid dosage form must identify the product and process characteristics that must be studied and incorporate specific validation tests to ensure that that product will meet all quality, manufacturing, and regulatory requirements.The validation should start with active pharmaceutical ingredient (API) characteristics so that this material will be uniform batch after batch, providing a solid footing upon which the dosage form will be built. Scientific information obtained during the preformulation stage can form the basis for a well-designed and comprehensive validation program. The parameters chosen must be relevant indicators of a controlled process. It is not sufficient merely to devise a test and set specifications for it; rather, it is desirable to show a cause and effect relationship between the parameter tested and control of the quality and/or process output.

For the tableting procedure, the steps studied include powder blending, granulation, particle size, and lubrication with compression, coating and drug release studies. Such step-wise studies have brought light into the impact of the parameters and their interactions and increased the understanding of the respective processes and also to collect a complete and rational database for the building of validation evidence.

It is concluded from the review that pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity and stability.

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