International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.1, pp 49-55, Jan-Mar 2012

# Guide to Inspections of Tablet Manufacturing Facilities including Pre/Post Approval Issues as per USFDA

**K. Pranitha, N. Vishal Gupta*, Shanawaz Anis, T.M. Pramod Kumar, K. Vaishnavi**

**Department of pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore – 570015, Karnataka, India.**

***Corres.author: vkguptajss@gmail.com***

**Abstract:** The objective of present study was to document the requirements for inspection of tablet manufacturing facilities as per USFDA (United States Food and Drug Administration) guidelines. US FDA guide provides information regarding the inspection and evaluation of the solid oral dosage form manufacturing facilities with greater emphasis on validation and evaluation of the validation of solid oral dosage form manufacturing and control processes. In addition these guidelines also brief about some issues associated with control of the manufacturing and the validation processes specific to some equipments such as Blenders, Dryers, Tablets and Capsule equipments, Coating equipment etc.
**Key words:** USFDA, Inspection, tablet.

## INTRODUCTION:

Audit and inspection are the most important functions of a manufacturing facility. The international standards organization (ISO) has defined quality audit as a "systematic and independent examination to determine whether quality activities and related results comply with planned arrangements, and whether these arrangements are implemented effectively and are suitable to achieve objectives." Self inspections should be conducted in order to monitor the implementation and the respect of good manufacturing practice (GMP) principles and to propose necessary corrective measures.

The inspection guide provided information regarding the inspection and evaluation of the manufacturing and control processes used to manufacture solid oral dosage form pharmaceutical products. The document provided guidance for the FDA investigator and promotes uniformity and consistency during the inspection and evaluation of the validation of the solid oral dosage form manufacturing and control processes.

It covers three phases of the validation process they are product development, design of the validation protocol,and demonstrationruns (validation) of the equipment and process in the manufacture of full scale commercial production batches.

Documented evidence includes the experiments, data and analytical results that support the master formula, the in-process and finished product specifications, and the filed manufacturing process. The development of a product and its manufacturing process and specifications, the design of the validation protocol,and the demonstration (validation) runs of the full scale manufacturing process requires scientific judgment based on good scientific data.

## Product development:

### A. Product development reports:

There is no statute or regulation that specifically requires a product development report, although companies are required to produce scientific data which justifies the formulation and the manufacturing and control processes.

The product development report should satisfy the needs of the company. Therefore, there is no specific format for the contents of the report.

Investigators must not list the absence or the poor quality of a product development report. The investigators should list or include the inadequacy of data to support the filed process and specific Master Formula filed. Investigators should review product development reports since they will reduce the time required to inspect the process.

**The development data found in these reports should include the following:**

**1. Drug substance characterisation:**

Characterization of the chemical and physical properties of the drug substance is one of the most important steps in the development of a solid dosage form. Chemical properties especially the identification of impurities are very important. In addition the physical properties like Solubility, polymorphism, hygroscopicity, particle size must be addressed.

Actual experience demonstrates that the physical quality, e.g. particle size of raw materials, can sometimes produce a significant impact on the availability and clinical effect of a dosage form drug. It is appropriate that the physical characteristics of a drug substance be characterized.

Development data will vary between new drugs and generics. In most cases the manufacturing process for a new drug substance (new chemical entity) is developed and scaled-up before the dosage form . Consequently, changes to the manufacturing process for the drug substance may change the purity profile or physical characteristics and thus cause problems with the finished dosage form.

Inspectional coverage should be given to the physical characteristics of raw materials, especially bulk drug substances, since they frequently affect the performance of the dosage form in which they are incorporated. This is particularly important for those drug substances that are poorly soluble in water.

Control of the physical characteristics of the excipient is also important because variations in such characteristics may also affect the performance of the dosage form. Changes in particle size of some excipients, for example, may affect content uniformity. In other cases, a change in the supplier of an excipient or lubricant may affect dissolution or bioavailability. In fact, the release of the active ingredients in some products is "timed" by varying lubricant blending time and concentration.

**2. Manufacturing Procedures:**

Procedures used to manufacture development batches must be specific and well documented. This is necessary for scale-up and subsequent comparison to the commercial process. This is another area where you will see differences between NDA/NADA and ANDA/ANADA products. The process used to manufacture the bio-batch must be well defined and well documented.

**3. In-process Testing:**

Specific specifications required to control the manufacturing process must be established and justified. This will require granulation studies which would include blend uniformity, sieve analysis, and moisture.

**4. Finished Product Testing:**

The monograph standards such as content uniformity, assay, hardness, friability, dissolution, and other are essential.

**5. Dissolution Profile:**

The dissolution profiles for the bio-batch or pivotal clinical batches should be evaluated in the product development report. There should be good correlation to the dissolution specifications and test results for the bio-batch/clinical test batches and the full scale commercial process.

**6. Stability:**

The Center for Drugs conducts an evaluation of the stability data and approves the expiration date. The product development report should contain an evaluation of the stability data that has been obtained. During post-approval inspections stability data is reviewed by the field.

### B. Pre-approval inspections:

Validation of three full size commercial lots is not required for approval of the application. The firm should have sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data and specifications form the basis for the validation protocol which may be developed following approval of the application.

The final step in the process is the demonstration runs proving that the process will perform consistently. Firms should validate the process using the specifications listed in the filing.

**To evaluate the proposed manufacturing process the following areas must be covered during the pre-approval inspection:**

**1. Master Formula:**

This document must include specific manufacturing directions for the full scale commercial process including in-process and finished product specifications.

Compare the process filed in the application to the process used to manufacture the bio/clinical batch. In some cases the process may be different after scale-up. This is acceptable if the firm has data showing the product produced by this process will be equivalent. Data such as granulation studies, finished product test results, and dissolution profiles are used to document that the two processes are equivalent.

**2. History Section of the Application:**

This section of the application is used to identify the biobatch or batches used for pivotal clinical studies. It is also useful for review of the correspondence between the firm and CDER/CVM.

**3. Development Data (Product Development Report):**

The firm cannot logically proceed to the validation step without some prior evaluation of the process. During the development phase the critical process parameters must be identified and specifications established. These predetermined specifications must be established during the development of the process.

This development data serves as the foundation for the manufacturing procedures, specifications and validation of the commercial process. In some cases, manufacturers have attempted to establish specifications such as hardness and particle size during validation.

It is important that the development and scale-up of the process be well documented so that a link between the bio/clinical batches and the commercial process can be established.

**4. Inspection of the Facilities:**

It is important that you physically inspect the facility to assure that the area and the ancillary equipment such as air handling and water systems are suitable for the proposed manufacturing process. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their impact on the overall compliance with GMP requirements. This includes facilities used for development batches and to be used for full-scale production batches.

**5. Raw Materials:**

The information contained in the Raw Material section under Product Development Report above. Inventory records are a good source for the identification of batches used for product development and bio-studies.

**6. Laboratory:**

The inspection of a laboratory requires the use of observations of the laboratory in operation and of the raw laboratory data to evaluate compliance with GMP's. Evaluate raw laboratory data, laboratory procedures and methods, laboratory equipment, and methods validation data to determine the overall quality of the laboratory operation and the ability to comply with GMP regulations.

**7. Equipment:**

At the time of the pre-approval inspection we expect that the equipment is in place and qualified. New products, particularly potent drug products, can present cleaning problems in existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

## Validation protocols:

Validation protocols are developed from the information obtained during product development research. These protocols list the specific manufact uring process and specifications that will be tested during the demonstration runs. Validation protocols are not required for the Pre-Approval Inspection but are required for Post-Approval Inspections.

## Demonstration runs (validation of the process):

**A. Test batch relationships:**

A "validated" process should produce a dosage form that is directly related to the dosage form on which equivalency and/or efficacy and safety were determined. This is usually the test batch. Therefore, compare the process used to make the test batch with the process that is used for routine full scale production batches. These processes and specifications must be equivalent. Typically the control of test batches includes, among others,

drug substance characterization, granulation analyses, and dose uniformity and dissolution profiles.

**B. Post-Approval Prospective Validation Inspections:**

In the post-approval, pre-marketing phase, we review the Validation Protocol and the Validation Report. Obviously, a Validation Protocol that lists all of the variables and parameters that should be controlled when the process is validated cannot be written until the variables are identified in the development phase. Failures of production size batches included dissolution, content uniformity and potency. Only through inspection and review of the facilities and raw data were the problems identified.

**Several parameters must be considered when evaluating the validation of an oral solid dosage form manufacturing process. They are:**

## 1. 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.

Review the raw material inventory records to evaluate the use of the drug substance in bio-batch, clinical, and/or test batches. Pay attention to the quantities and source of materials used and the testing performed. 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.

## 2. 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 exist which hope fully will be shown to perform consistently and produces products in compliance with predetermined specifications.

**The importance of specific written directions and specifications cannot be overemphasized. Problem areas may include:**

1. The failure to specify the amount of granulating solution, resulting in over wetting and dissolution failures of aged batches.
2. The failure to specify the encapsulation machine and operating parameters, such as dosing discs, resulting in weight variation failures.
3. The failure to specify the compression machine(s) and operating parameters, resulting in content uniformity failures.

In addition tothe concern about specific manufacturing directions, equipment presents its own set of unique problems which have to be considered in the control of the manufacturing and the validation processes.

**Some issues may associated with the equipment they are:**

**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.

**1. Pony Pan Type:**

This mixer has historically been used for the manufacture of wet granulations. Because of its open pan or pot, granulating agents, such as starch paste, could be added while mixing. Since it is usually open at the top to allow the mixing blades to penetrate the powder, mixing operations are usually dusty and can lead to potential cross-contamination problems.

The usefulness of these mixers is limited to wet granulating. With this type of mixer, there is good horizontal (side to side) blending. Vertical (top to bottom) mixing does not occur. Powder placed in the mixer first will be poorly mixed. Segregation or unmixing is also a recognized problem.To minimize this problem, some manufacturers have emptied the pan contents half-way through the mixing cycle in an attempt to turn the powder over at the bottom of the mixer. To all eviate the problem of the lack of mixing along the sides or walls of the pan , manufacturers have utilized a hand-held steel paddle at various times during mixing. This type of mixing is difficult to control and reproduce. Thus, it would be difficult to validate.

**2. Ribbon Blender:**

1. In the ribbon blender, powder is mixed both horizontally and vertically.
   Loading operations can be dusty.
2. The major and potentially the most serious problem with the ribbon blender is that there is a "dead-spot" or zone at the discharge valve in some of these blenders. To overcome these manufacturers have to recycle the powder from this area at some point during the mixing process. Another concern with this mixer is the poor mixing at the ends of the center horizontal mixing bar and at the shell wall because of blade clearance.
3. Cleaning problems, particularly at the ends of the ribbon blender where the horizontal bar enters the blender, have been identified.If manufacturers do not disassemble and clean the seals/packing between batches, they should have data to demonstrate the absence of foreign contaminants between batches of different products processed in the blender.

**3. Tumbler Blender:**

- Common mixers of this 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. Powders may also clump due to static charges and segregation can occur. Low humidity can contribute to this problem.
- Blending under very dry conditions has been found to lead to charge build-up and segregation, while blending of some products under humid conditions has led to lumping.

**4. High Shear (high energy) Mixers:**

- These mixers are highly efficient and ideally suited for wet granulations. The mixing vessel is enclosed, and dust only enters the environment when loading.
  One of the problems associated with these mixers is the transfer or conversion of products blended in the older types of mixers to these blenders. Mixing times are going to be different, and the physical characteristics of the blend may also be different
- These mixers are very efficient. 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 up on drying as a different physical form.
- A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat that can sometimes result in charring of some sugar base granulations.

**5. Plastic Bag:**

- Firms have resorted to the blending or manufacture of a trituration in a plastic bag. It is very difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. The use of a plastic bag can not be justified in the manufacture of a pharmaceutical product.
- When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed.

**b. Dryers:**

There are two basic types of dryers. One is the oven dryer where the wet granulation is spread on trays and dried in an oven. The second dryer is fluid bed dryer in which the wet granulation is "fluidized" or suspended in air. The fluid bed dryer yields a more uniform granulation with spherical particles. This may result in compression problems that may require additional compression force.Other issues concern with drying includes moisture uniformity and cross contamination.Tray dryers present more moisture uniformity problems than fluid bed dryers. 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 fluidbed dryers, moisture problems can occur if the granulation is not completely fluidized.

**c. Tablet Equipment:**

- Another important variable in the manufacturing process is the tablet press or encapsulating machine.The newer dosage form equipment requires granulations with good flow characteri stics 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.
- With regard to the newer computer controlled tablet compression equipment, buckets of tablets are often rejected because of potential

weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be investigated. Reworking processes must be validated.

**d. Coating Equipment:**

Most of the 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 volumeof coating solution, rate and temperature can be controlled by some of the more highly automated operations.

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 are all parameters that need to be addressed. Another problem associated with the coating process concerns the heat applied to products that are sensitive to heat.

Examine processing records for specificity in the identification of critical steps in the coating process. It is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and to control the parameters of the coating process.

**3. 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 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.

This is particularlyimportant for the comparison of the bio-batch with production batches and also, when processes are modified or changed.

Another test which is typically performed on the granulation, particularly when the wet granulation process is used,is loss-on-drying (LOD) and/or moisture content. If organic solvents are employed, then residual solvent residues are also tested. In the validation of a drying process, LOD levels are determined prior to, during and after drying in order to demonstrate times and levels.

**4. In-Process Control/Testing:**

The purpose of this document, in-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency through out these operations.For tablets, individual tablet weights, moisture, hardness 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 dosage unitweights performed throughout compression /encapsulation.This is particularly important for capsule products

Hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate both equivalency and consistency.

**5. Test Results with Validated Methods:**

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.

**6. Investigations/Product Failures:**

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.

When reviewing a validation report, the basis for concluding that a process is satisfactory, particularly those with failing results, should be evaluated.

**7. 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.

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[1,2].

## CONCLUSION:

From the above review, it can be concluded that the guidelines for inspection according to the various regulatory agencies gives information about almost the similar requirements and instruct to follow same procedure. Except for guidelines provided by USFDA, none of the other guidelines specifically discuss about inspection iof tablet manufacturing facility but still the information provided by the guidelines are useful for inspection of the tablet manufacturing facility.

## REFERENCES:

1. Quality assurance for pharmaceuticals-A compendium of guidelines and related materials, Vol.2; 2nd updated edition; 2007; 285-347.

2. USFDA-Inspections,Compliance, Enforcement, and Criminal Investigations, Oral Solid Dosage Forms Pre/Post Approval Issues (1/94), Guide to inspections of oral solid dosage forms pre/ post approval issues for development and validation, January 1994.

*****