

GUIDE TO INSPECTIONS OF ORAL SOLID DOSAGE FORMS PRE/POST APPROVAL ISSUES FOR DEVELOPMENT AND VALIDATION

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I INTRODUCTION

This inspection guide provides information regarding the inspection and evaluation of the manufacturing and control processes used to manufacture solid oral dosage form pharmaceutical products. This document provides 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; product development, design of the validation protocol, and demonstration runs (validation) of the equipment and process in the manufacture of full scale commercial production batches.

Although this document it is not all inclusive, it addresses many of the issues and examples of validation problems of oral solid dosage forms which investigators and analysts may encounter. The inspection team is expected to review other agency documents in preparation for these inspections.

The Validation Guideline issued by the agency in 1987 defines process validation as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

The three components of this definition include documented evidence, consistency, and predetermined specifications. 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.

With regard to consistency, several batches would have to be manufactured, using the full scale batch size, to demonstrate that a process meets the consistency test. At least three batches are needed to demonstrate consistency.

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 judgement based on good scientific data. We expect that in-process control and product specifications will be established during the product development process, with the test batch serving as the critical batch used for the establishment of specifications.

Specifications, such as hardness and particle size, should be established prior to validation of the process; these specifications should be included in the validation protocol. The use of product development runs of the process to establish both specifications and demonstrate that the system is validated often causes problems. In these cases, more in-depth inspection and evaluation will be required; some of these process runs often produce failing product because the product specifications

have not been fully established and tested.

The inspection team should observe facilities, equipment and processes to put data review in proper context. It is also important that raw data, including validation and laboratory logbooks be audited or reviewed to verify accuracy and authenticity.

II BACKGROUND

Two common complaints regarding validation issues frequently have been raised. The first concerns the misconception that the 1987 validation guide represents a new requirement. The second concerns the lack of specificity in the agency's guides. In 1978, the Current Good Manufacturing Practice Regulations were revised and provided for process validation. Therefore this guideline does not represent a new requirement. The regulation is nearly 15 years old.

Both the agency and the industry have recognized the need to establish general guidance for the validation of manufacturing processes, and the agency published a draft guideline in March, 1983. However this draft guideline was a very general document addressing general principles and was applicable to sterile and non-sterile drugs and devices. In March, 1984, it was reissued as a draft guideline, and was finalized in May, 1987.

The 1987 validation guideline merely points out the need to adequately develop and control manufacturing processes. It discusses microbiological issues and provides few specific and practical applications for the validation of manufacturing processes for a marketed solid oral dosage form.

The issue of retrospective validation, and its application to marketed products, is frequently encountered. This concept of using historical data (test results), along with process control and process specificity was of value until more scientific methods for demonstrating process validation evolved. It should be pointed out that retrospective validation is not merely the review of test results. It also requires that the manufacturing process be specific and the same each time a batch is manufactured. Thus, specific raw material specifications (including particle size when necessary), in-process specifications (tablet hardness, etc.), and specific manufacturing directions are required. Obviously, any failing batches attributed to the process would necessitate the conclusion that the process is not validated and is inadequate.

Prospective process validation is required, particularly for those products introduced in the last 7 to 8 years, or those for which manufacturing changes have been made. However, in some cases where older products have been on the market without sufficient pre-market process validation, 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.

III 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. Most companies have used product development reports, technology transfer reports, and others to summarize the scientific data that justifies the product and process. The product development report should satisfy the needs of the company. Therefore, there is no specific format for the contents of the report.

It is suggested that the company develop a product development SOP which describes the development process, the documentation requirements, and the individuals responsible for approving

the filed process. This SOP can be brief and again there is no legal requirement that companies produce such an SOP.

Investigators must not list the absence and or the poor quality of a product development report on the FDA 483. The investigators should list or include the inadequacy of data to support the filed process and specific Master Formula filed. It is not a GMP deficiency nor is it a filing requirement to have a formal Development Report. 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 Characterization

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 of the BPC such as solubility, polymorphism, hygroscopicity, particle size, density, etc. must be addressed.

The literature, and 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. Therefore, it is appropriate that the physical characteristics of a drug substance be characterized, that the impact of the physical characteristics be determined and that a specification for the bulk drug product be established if necessary.

Development data will vary between new drugs and generics. Characterization and establishment of specifications for the drug substance is one example. In most cases the manufacturing process for a new drug substance (new chemical entity) is developed and scaled-up before the dosage form. In early development stages very little information is available regarding polymorphic forms, solubility, etc. 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. Although these types of problems are expected, the firm must investigate and document batch failures for the BPC and dosage form product.

On the other hand the generic manufacturer usually purchases the drug substance from a BPC manufacturer who may not be willing to supply information regarding the synthesis or analysis of the drug substance. Therefore, the finished dosage form manufacturer must perform the appropriate test to characterize the drug substance chemically and physically and establish appropriate specifications. This may require developing analytical methods to identify impurities. In some cases this information can be obtained from literature searches.

In either case it is important that the firm compare the drug substance used to manufacture the bio-batch or clinical batch(es) and the drug substance used for the commercial batches. Therefore, review the specifications, analytical methods, and test results for the lots of the drug substance used to manufacture these batches. Remember that the safety of the drug may be based upon the type and level of impurities and different physical characteristics may affect dissolution or content uniformity.

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.

For those products on which biostudies were conducted, the physical characteristics of the drug substance used for the study should serve as the basis for the physical specifications.

It is widely recognized that when discussing in-vivo release rates and drug absorption rates, fast, immediate release is not always best. For some "immediate" release drug products, such as carbamazepine tablets, a slower release is desired. Therefore, it is frequently desirable to have minimum and maximum particle size specifications to control the release rate. For example, micronizing or milling a drug substance and providing greater surface area of the substance may also result in faster dissolution and possibly faster absorption and higher blood levels. Such changes to "improve" the dissolution may not always be desired.

In addition to release or dissolution, variation in particle size, particle shape, and/or bulk density can also have an effect on the uniformity of dosage forms, particularly those manufactured by direct compression or direct encapsulation.

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing, as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling.

Some manufacturers have established wide ranges for specifications. Investigators should review these specifications from a GMP and validation perspective. Even though a wide range for a physical specification, such as particle size or surface area may be established in a filing, it is expected that such ranges be verified in the validation of the process. In a recent court decision the judge ruled that companies cannot hide behind the approval of processes listed in an application when these processes do not work. In other words the approval of the filing has no impact on processes that do not perform consistently.

For example, in a filed process it was determined that particle size would have no effect on drug absorption and dissolution and a wide range particle size specification was established. However, in the GMP review, it was found that variation in particle size had a major effect on content uniformity. Therefore, a tighter particle size specification had to be established.

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. The literature contains many examples of lubricant processing causing major changes. Such changes in excipients illustrate the deficiencies with the utilization of retrospective validation because, for such validation to be satisfactory, control of all parameters and key steps in the process are necessary.

The control of mixing times and physical characteristics of all ingredients is critical to successful validation of all formulations and processes. A major question that must be addressed is the need for testing physical characteristics (particle size) for each batch of excipient. For many single source excipients, particle size is a supplier specification and is usually tightly controlled. Having established a specification and not testing each lot of excipient upon receipt may be satisfactory in such cases. However, for some multi-source excipients and where the dosage formulator expects to shift sources of supply, there may be differences in physical characteristics (particle size) that may have an effect on dose uniformity and dissolution. Examine the practices with respect to the source of supply of the key excipients and determine if there is justification for the lack of testing lots of excipient for physical characteristics.

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. In the case of the NDA/NADA you will see several clinical and/or test batches manufactured over a period of time and you would expect to see changes in the process as more is learned about the drug and the process. The level of documentation should increase as the process becomes more defined and the firm begins phase II and III studies.

The generic product focus is on the biobatch. Again the process used to manufacture the biobatch must be well defined and well documented. Also the firm should have worked with the process by means of test batches so they can reproduce the biobatch. Therefore you would expect to see more than one batch made at this stage of the development process.

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. Read the section under, "Demonstration Runs of the Process (Validation of Process)" for more information.

4. Finished Product Testing

Testing for the monograph standards such as content uniformity (when a specification applies), assay, hardness, friability, dissolution, and others are essential.

5. Dissolution Profile

The dissolution profiles for the biobatch 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 biobatch/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. Therefore, the investigator must audit underlying raw data and analytical worksheets to assure the accuracy and authenticity of stability data contained in summary reports.

B. PRE-APPROVAL INSPECTIONS

Validation of three full size commercial lots is not required for approval of the application, however the firm must have data that justifies the full scale commercial process filed in the NDA/ANDA or NADA/ANADA application. In other words, 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 (validation) 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. One of the basic objectives of our review is to identify the biobatch. Also, any batches in which in-vivo studies were carried out, and particularly those which in-vivo studies showed inequivalency should be reviewed.

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, with the biobatch or pivotal clinical batch serving as the reference batch.

Development of a solid dosage form will vary from firm to firm and will be dependent upon the specific product and process. However, the formula ranges, physical and chemical specifications of the drug substance and excipients, in-process variables, interaction effects of the dosage form ingredients under normal and stress aging conditions, should be confirmed by limited challenge in pilot-scale and production-size batches.

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. However, as the validation definition states, specifications must be determined prior to validation of the process.

When a manufacturer files a manufacturing process in an application, we expect that the process will yield a product which is equivalent to the product on which the biostudy or pivotal clinical study was conducted. Therefore, 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. The firm should have data such as granulation studies, finished product test results, and dissolution profiles which may be used to document that the two processes are equivalent.

In most cases in vitro data alone will not be sufficient to document equivalency. Determine if an equivalency evaluation has been made. This bioequivalency evaluation must be made by qualified individuals, and the firm should have a signed statement documenting that the processes are equivalent. Therefore, in many cases you may see an in-vivo bioequivalency study performed. Obviously, the firm cannot provide this type of data if they have not manufactured pilot or test batches

using the types of equipment and controls specified in the proposed master formula.

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

Review 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 biostudies.

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 and to specifically carry out the commitments in an application or DMF.

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. (Refer to the Laboratory Inspection Guide for additional discussion).

Many of our inspections have identified foreign peaks and impurities not filed or discussed in applications. Also, many of our inspections have shown laboratory test methods not to be validated. The transfer of laboratory methods and technology from the Research and Development Department to the Quality Control Department should be reviewed.

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. (Refer to the Cleaning Validation Inspection Guide for additional discussion).

IV VALIDATION PROTOCOLS

Validation protocols are developed from the information obtained during product development research. These protocols list the specific manufacturing 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.

Key processes and control specifications should have been established during product development research and should be carefully listed in the validation protocol.

V 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. Therefore, the importance and the need for good control of the manufacturing process used to produce the test and clinical batches cannot be overemphasized. Typically the control of test batches includes, among others, drug substance characterization, granulation analyses, and dose uniformity and dissolution profiles.

The validation report should compare the manufacturing processes and specifications for the test batches to the full scale batches. However, such a finding may be contained in other documents. Request any evaluation that has been conducted on the equivalency of these batches and processes and review any tabulated data that shows the processing equivalency between the biobatch and validation batches.

B. Post-Approval Prospective Validation Inspections

Inspection team members must reread the sections under Part I Product Development which will not be restated under this section. Those sections contain information that is key to the evaluation of the validation process.

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.

In many of our post-approval, pre-marketing inspections, validation (and consistency) could not be established. Failures of production size batches included dissolution, content uniformity and potency. Validation reports on batch scale-ups may also reflect selective reporting of data. 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. For example there are at least eight major areas that must be included:

- o Biobatch Relationship
- o Raw Materials
- o Manufacturing Procedures and Equipment
- o Granulation/Mix Analysis
- o In-Process Controls
- o Test Results with Validated Methods
- o Investigations/Product Failures
- o Site Review

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 biobatch, clinical, and/or test batches. Pay attention to the quantities and source of materials used and the testing performed.

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.

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 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:

- o the failure to specify the amount of granulating solution, resulting in overwetting and dissolution failures of aged batches
- o the failure to specify the encapsulation machine and operating parameters, such as dosing discs, resulting in weight variation failures
- o the failure to specify the compression machine(s) and operating parameters, resulting in content uniformity failures

In addition to the 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. 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.

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. However, 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 alleviate 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.

The potential for segregation and poor mixing along the sides and particularly the bottom of the pony blender makes this type of blender less desirable for the dry blending of granulations of drug products. Consequently, whenever such dry blending is encountered, the investigator should be alert to potential problems with blending validation and content uniformity. Whenever in-process samples of the granulation are collected as part of an investigation or inspection, the formula card along with the weight of the dosage unit to be manufactured is needed for calculations.

2. Ribbon Blender In the ribbon blender, powder is mixed both horizontally and vertically. Loading operations can be dusty. However, during the actual blending, it is enclosed, thereby limiting the amount of dust generated to the environment.

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 compensate for this "dead-spot", manufacturers have to recycle the powder from this area at some point during the mixing process. Obviously, there should be adequate and very specific directions and procedures for assuring this critical step is performed. Verify that this step is included in the directions.

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. The level of powder placed in this mixer is normally at the top of the outer ribbon blade, and as with other mixers, care must be taken not to overfill the mixer.

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. More so than with other mixers, powder charge levels should not exceed 60 to 65% of the total volume of the mixer.

Fabricators of tumbler type blenders identify the volume as the actual working capacity and not the actual volume of the blender. It is important to correlate the bulk density of the granulation with the working capacity of the blender.

4. High Shear (high energy) Mixers There are several fabricators of these mixers that include GRAL, Diosna and Lodge 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. 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 upon drying as a different physical form.

The presence of an intensifier bar in the center of the blender which rotates at very high speeds breaks down smaller, harder agglomerates. 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. It should be pointed out that these same comments are applicable to other high energy mixers which also rely on high speed choppers to disperse powders. Also, cleaning of the blender requires disassembly of the intensifier bar between products.

5. Plastic Bag Any discussion of mixers would not be complete without addressing the plastic bag. Firms have resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, 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 cannot 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. In a recent inspection, a firm was noted to manufacture a small 5 kg. size batch of a tranquilizer. Because all of the firm's blenders were of much larger capacity, an inquiry was made as to the mixer employed. Although the processing records indicated a large blender was employed, it was later determined that the batch was actually blended in a plastic bag.

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 the 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. However, such a change should be examined for equivalency with in-vitro testing such as hardness, disintegration and comparative dissolution and stability testing conducted.

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.

Regarding cross contamination, oven dryers, particularly those in which air is recirculated, present cross contamination problems because air recirculates through a common filter and duct. For fluid bed dryers, the bag filters present cross contamination problems. In order to minimize problems, manufacturers use product dedicated bags.

c) Tablet and Capsule 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 characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require a uniform granulation to function correctly. Setup of the microprocessor controlled tablet press usually

includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will alarm when the lower or high weight tablet is compressed.

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.

Many unit operations now provide for blending in totes with discharge of the tote directly into tablet compression equipment. Because of segregation problems at the end of discharge, tablets from the end of compression should be tested for content uniformity. The use of inserts in totes has been shown to minimize segregation.

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.

With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations, requires humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products has also presented some problems because of the different types of encapsulation equipment. Older equipment that operated on gravity fill, such as the Lilly and Parke Davis machines, was commonly used for manufacturing capsules in clinical manufacturing areas. When formulations were scaled-up to high speed encapsulation equipment, flow problems and poor weight variation resulted. Additionally, some of the newer equipment provides for the formation of a slug which could impact on dissolution.

As previously discussed, set-up and review of operating directions should be covered in inspections. The investigation by firms of weight variation problems should also be covered. Many firms, in order to recondition (rework) batches, pass those particular batches through a sorter, such as the Mocon Vericap. This machine works on the principal of current (dielectric constant), and moisture variation in the filled capsules can cause inaccurate results. Check the data used to qualify equipment and investigate the equipment log for this sorting machines to identify batches with weight problems that were processed in it. The data supporting the accuracy of equipment to reject low or high weight capsules should be reviewed.

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.

With respect to poor disintegration, Ferrous Sulfate tablets probably represents the classical example. Over the years, there have been many recalls from many different manufacturers for poor disintegration of coated Ferrous Sulfate tablets. Likewise, there have been many problems with poor dissolution attributed to the coating process. Again, the shellac undercoat hardens, and even sometimes cracks, resulting in poor dissolution.

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. For example, the temperature 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.

There are a few products, such as some of the antihistamine tablets, in which the drug substance is applied during the coating process. Other products require the active drug substance to be applied as a dust on tacky tablets as part of the coating process. For these products, it is particularly important to apply the drug in the coating solution in many controlled applications.

Examine processing records for specificity in the identification of critical steps in the coating process. Review the firm's data demonstrating that critical steps are consistent and reproducible.

Again, 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 (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 devices 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. A sampling device for sampling dosage unit weights is also available in Cincinnati District for use by investigators.

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 compendial 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.

In addition to analysis of blends for dose uniformity and potency, blends are tested for physical characteristics. A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for the comparison of the biobatch with production batches and also, when processes are modified or changed. The particle size profile will provide useful information for demonstrating comparability.

Particle size profiles are particularly important for the tablet made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet and have an effect on dissolution. For example, a recent dissolution failure was attributed to a change in the milling screen size, yielding a granulation with larger granules. Since it was a coated tablet, larger pores permitted increased penetration into the tablet by the coating solution, resulting in slower dissolution.

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. As with processing variables, levels (specifications) are established in the development phase with the validation phase used to confirm the adequacy of the process. As with other specifications and processes, the investigator should review the data used to support the drying process and determine the significance (if any) of variable drying times and levels.

4. In-Process Testing

For the purpose of this document, 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.

With regard to individual capsule weights, a major question that arises concerns acceptable levels. Since most USP assay limits are 90 to 110%, it would seem reasonable that each unit manufactured comply with these specifications. It should be pointed out that 85 to 115% limits are established by the USP for variability in both blending and compression or encapsulation operations.

Since hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate both equivalency (comparability) and consistency.

With regard to moisture, some tablets have set up upon aging as a result of poor moisture control and inadequate specifications. For example, this has been shown to be a major problem with Carbamazepine tablets.

5. 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.

6. 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.

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.

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.

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