DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(6&7), 1119-1133 (1989)

VALIDATION OF SOLID DOSAGE FORMS
THE FDA VIEW

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ABSTRACTS

In May 1987 the United States Food and Drug Administration published the final version of a guideline for process validation for pharmaceutical manufacturing. The document incorporated the comments from the pharmaceutical industry gathered after the publication of three draft versions in 1983, 1984 and 1986.

The presentation will cover the current definition of process validation as well as terms such as "worse case" and "installation qualification".

The stages of process validation will be discussed including the written plan (protocol): records to be maintained; suitability of raw materials; equipment performance qualification; the number of runs required; and acceptance criteria.

Specifics for solid dosage forms will be presented along with details on batch record in instructions and establishment of acceptable range limits.

Circumstances and requirements for revalidation will be discussed as well as the validation of current finished dosage forms by retrospective validation.

INTRODUCTION

In May 1987 the United States Food and Drug Administration published the final version of a quideline for process validation for pharmaceutical manufacturing. The document incorporated the comments from the pharmaceutical industry gathered after the publication of three draft versions in 1983, 1984 and 1986.

The presentation will cover the current definition of process validation as well as terms such as "worse case" and "installation qualification." The stages of process validation will be discussed including the written plan (protocol); records to be maintained; suitability of raw materials; equipment performance qualification; the number of runs required; and acceptance criteria. Specifics for solid dosage forms will be presented along with details on batch record instructions and establishment of acceptable range limits. Circumstances and requirements for revalidation will be discussed as well as the validation of current finished dosage forms by retrospective validation.

Validation:

The concept of validation, in connection with the manufacturing of drug products, became prominent about 10 years ago. This was when the United States Food and Drug Administration revised the regulations which control the manufacture of pharmaceutical products. These are known as the current good manufacturing pratice regulations, commonly referred to as the <<GMP'S >> or the CGMPS.

In 1978 the word << VALIDATION >> appeared for the first time in several specific sections of the GMP regulations. Although the Good Manufacturing Practice regulations contained a

section titled definitions, the word validation was not one of those terms that was defined.

The first written definition for the word << VALIDATION >> was in an internal FDA document called a compliance program. This is a type of standard operating procedure for the FDA. That first FDA definition of validation was simple and uncomplicated: "A validated manufacturing process is one which has been proved to do what is purports (or intends) to do".

In the intervening nine years, this basic definition of validation has been revised, refined and expanded into this version which now appears in the current FDA validation guideline: "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics".

A look at this latest definition shows how it differs from the earlier version. The word << MANUFACTURING >> was removed and the order of the words reversed. The phrase validated manufacturing process now became << PROCESS VALIDATION >>. This definition has three major aspects. First, it has to be documented evidence that is, in written form. Secondly, it must provide a <<HIGH DEGREE OF ASSURANCE>> that the process will work properly- notice that this does allow some flexibility. It does not say that you must absolutely provide assurance that the process will work properly. It says a high degree of assurance. The definition continues with a reference to a specific process that will (and here is another important word) << CONSISTENTLY >> produce products which meet the specifications. One other interesting point is that FDA offers this as << ONE DEFINITION >> of validaiton. They do not say that this is the only definition.

Now that we have defined the term validation, we must go on to briefly define the term << GUIDELINE>>. Then we will join the two words together to arrive at our subject, the FDA validation guideline. Guidelines are addressed in a section of the USA

Federal Regulations. There are some general elements that apply to all FDA guidelines. First, they are not legal requirements. Guidelines are the formal position on what practices are acceptable to the Food and Drug Administration. We should also note that the Drug Manufacturing Industry is not required to follow these guidelines. This is what makes guidelines different from regulations.

Since FDA wanted this validation guideline to apply to both drugs and medical devices, the concepts are broad rather than detailed and specific as in some other FDA Guidelines. By writing general requirements, FDA has given drug manufacturers sufficient freedom within these road outlines to tailor the validation to their own processes. This is consistent with the policy of the Food and Drug Administration to set goals for drug manufacturers by communicating what needs to be done rather than telling them how to do it.

There were several circumstances that let to having FDA issue this validation guideline. While testing of the finished product does play a major role in assuring product quality, testing of the finished product, by itself, does not provide enough assurance. Further nearly all drug testing destroys the product being tested and so must be limited to tests on small portions of the lot. However, these samples may not represent the nature of the entire lot.

These shortcomings have led to a phrase that we hear often, but is nevertheless true, that quality cannot be tested into a product but must be built in along the way. FDA determined which controls were currently used by some of the more advanced pharmaceutical companies and combined these along with some other requirements into this General Validation Guideline. The drafts of 1983, 1984 and 1986 were published to allow review and comment by all interested persons. With this feedback, the document was refined and issued in final for in May 1987. While valuable information is provided in the Validation Guideline, we should keep in mind that it gives only minimum considerations for a good

validation program, just as the current Good Manufacturing Practice regulations are also minimum requirements.

Turning back to the Validation Guideline itself, the first requirement is to have a written plan or protocol which itemizes the tests to be performed and the data to be collected. As the guideline defines the term: The "validaiton protocol" is a written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

In writing this plan, ask yourself, <<what are the consequences if one aspect of the operation falls outside of its range? >>. Then take that aspect, combine it with other stages and look for possible interactions. Keep a well organized set of validation documents. As you proced, there should be a concise summary of the results of the study, not only for each phase but also for the operation as a whole.

The raw data which support the conclusions in the summary do not have to be filed with the summary documents, but should be readily accessible. For example, if you reviewed 50 batch records during the validation process, these should be identified in such a way that they can readily be retrieved from the files. FDA will look at a number of these documents to verify that the summary is truly representative of the process that was validated.

Retrospective Validation

Timing of the validation is a factor that will determine what type of information can be gathered. While the type of formal validation program that we are considering has been used for about 1h years, many of the drug products that must be validated have existed for a much longer time. It is not surprising that "retrospective validation" is used most frequently. As defined in the guideline retrospective validation is : "validation of a process for a product already in distribution based upon accumulated production, testing and control data".

Initially some drug manufacturers held the view that manufacturing a product for an extended time was equivalent to validation. They are the people who say, << we have been making this tablet for 20 years so it must be ok >>. While there may be certain amount of truth in this idea, they may have just had luck in avoiding problems. You really need to be assured that each step in the process will be consistent as long as the drug is manufactured. It seems to me that retrospective validation offers A number of advantages, the main one being that the raw data for the most part is already present in the form of what can be called historical data. What must be done with this raw data however, is that it must be sorted and it must be well organized. Retrospective validation calls for reviewing the accumulated records for the production process, controls, and testing and then statistically analyzing any variance.

Prospective Validation

While retrospective validation can be done successfully, production of a new product offers the greatest opportunities for complete process control. Then we can consider "prospective validation". As defined in the FDA guideline: "prospective validation is validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics".

Prospective validation is divided into two major phases; equipment installation qualification and process performance qualification. Both terms are defined in the FDA guideline. "installation qualification" is establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.

It does seem logical to begin with validation of the production equipment to ensure that it is capable of consistent operation. If you cannot depend on the proper functioning of the

equipment, you cannot proceed with validation. The guideline cautions that you should be sure to include people from various departments in these initial assessments such as engineers and quality assurance representatives as well as production people. Once you decide which pieces of equipment will be used, you can begin to write down those aspects of its operation that could affect the process and product.

FDA looks for a calibration record for each separate adjustable component on a machine. For example, an extruder for tablet granulations may have a speed control or a timer. For a speed control, we would expect that someone at the firm would measure the actual revolutions per minute of the machine and write down the actual speed compared to the speed indicated on an indej or dial. Then, calibration should be done and the appropriate index speed fixed for each extrusion operation. When such a calibration operation is carried out, the raw data obtained when making the measurements must be retained and be available for review. However, the certificate of calibration only needs to have a reference to this calibration procedure. The same would apply to a timer. You would perform an independent time study and determine the precise accuracy of the timer and list any appropriate correction factors on the batch product and control record.

For any piece of equipment you would also want to verify the utility supply--does it have the correct electrical voltage and current capacity? perhaps air pressure of hydraulic pressure is needed to eparate a machine. Will there be a sufficient supply if two or more machines are connected to the same supply lines? we once found a problem with equipment requiring steam for its operation. When any one of three pieces on the manifold was operated, the steam pressure was sufficient. But when all three were turned on at the same time, the pressure dropped below a usable level.

Tablet coating pans are another area where you may wish to monitor the temperature of the incoming air with a thermocouple

or other appropriate temperature measuring device. You may need to know the consistency of the temperature at various stages during the coating cycle. Likewise, an air flowmeter would determine the optimal flow of air needed for tablet coating. For mixers and blenders, the speed of operation may be critial if you have drug products that are very potent at low dosage levels. You should establish appropriate calibration limitations. If you change to a different type of blender, the process should be revalidated.

What about the raw materials or components used for these validation runs; in general, you should use the actual ingredients that will be used in the finished tablet. You can perform your test run and if it does turn out to be successful, the material can be used for regular production. Raw materials or components are an important area of consideration for validation of solid dosage forms. Some raw material attributes can be directly related to availability of the drug within the human body. Be sure to determine whether your products contain raw materials that can affect bioavailability.

For active raw materials, all physical attributes should be characterized. As you may know, micronizing of an active ingredient can have a major affect on the way it reacts once it enters the human body. Other important aspects are particle size and bulk density. Variations in the crystalline structure of the substance can also affect the tabletting process and, in some instances, lead to a variation in tablet hardness. If any of your ingredients are available in more than a single crystalline form, special care should be given when specifying the grade of that material that you require from your suppliers. Also be alert to these differences as you test samples of the incoming raw materials.

Still another area for care and concern is the microbiological cleanliness of each raw material. Some of the ingredients commonly found in tablets are susceptible to microbial contamination, pnarmacopeia such as the united states pharmacopeia (USP) specify

appropriate tests for determining the cleanliness of the raw material.

Raw material supplies play a major role in assuring raw material quality. If like many companies you use a variety of raw material suppliers, are you sure that all sources supply material with the same characteristics? extensive testing, both physical and chemical, should be done on material coming in from any new supplier, to ensure that the material behaves essentially the same as that ingredient utilized during validation of the manufacturing process. The safest approach, of course, is to revalidate the procedure with any initial change in a raw material supplier. This in fact is what FDA suggests in the Validation Guideline.

Once a material from a new raw material supplier has been properly qualified and evaluated, a certificate of assay should be requested for all subsequent shipments of that material. This will help to insure that the physical and chemical characteristics will remain essentially the same. This is particularly important as many suppliers in turn purchase the material elsewhere and their source of supply may vary. However, as you are the one making the tablet, you must make sure that the materials are consistent from lot to lot.

As I see it, the validation runs differ from the ordinary runs in that you will be paying much closer attention to every aspect of the process. You will be taking samples more frequently, and subjecting the samples to more intensive analysis than you would ordinarily. You will be double-checking on the calibration of the various instruments and the operation of each system interacting as a whole. If it is a new piece of equipment, you will want to perform the installation qualification before the calibration, many times, a representative from the manufacturer or supplier of the equipment can be present for the installation qualification. They can be very useful if the set-up and operation is complicated. The manufacturer's representative is usually in the best position to also advise on maintenance and adjustment

of the equipment. As you carry out the equipment qualification testing, you will want to challenge the equipment by varying the parameters to determine what effect, if any, this would have on routine manufacturing.

Worst Case

This is a good point to consider another concept covered in the FDA Validation Guideline, that of the worst, case. Because of controversy regarding the scope of this term, FDA has included it in the definitions: "worst case" - a set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest change of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

For example, if you were varying the speed of a blender to see what effect it may have on the process, you would not run it so fast that the powder was thrown out of the machine. You would vary the speed sufficiently while taking samples to determine the outer limits of the Revolutions per minute. Then you could set your operating range well within these limits to assure reproducibility. Other pieces of equipment you might be qualifying include various pumps such as those for spray nozzles to determine the liters per minute capacity of the pump, verify the spray rate and determine the fluctuation in air pressure.

Granulation drying ovens should be validated so that you are aware of the temperature variations within the cabinet. These can be verified by placing thermocouples in the dryer. Then compare the thermostat input setting to the temperature actually reached within the dryer. The actual temperature should then be compared to that traced on the chart recorder. Depending on the results, you may have to relocate the chart recorder probe to the coldest spot in the dryer to ensure adequate drying time and temperature.

In the course of these validation procedures, all acceptance criteria must be met. However, a failure can occur at any stage. If this happens, the most important thing is to carry out a careful investigation to determine the cause of that failure so that the situation is unlikely to reoccur. Information from these equipment qualification procedures should be used as a basis for written standard operating procedures for calibration and maintenance. One of the most important aspects is to designate a specific person to be responsible for carrying out the calibration and maintenance for each piece of equipment.

One of the more successful calibration reminder systems I saw consisted of a simple wall calendar hung in a place which all employees passed. An entry for each week showed who was responsible for the maintenance and which piece of equipment was involved. One aspect in regard to equipment that is sometimes overlooked is the cleaning and calibration needed after repairs have been made. Depending on the type of repairs carried out, the cleaning process may need to be more extensive than usual. The same applies to the calibration procedure. Depending on the type and number of parts replaced, calibration ranges may change significantly.

One question that is raised often is, how many runs are needed to perform acceptable validation? in earlier drafts on the validation guideline, FDA wrote that a minumum of three runs should be performed. However that reference was deleted in the final version because it did not apply to all circumstances. The final guideline notes that tests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results. The guideline suggests that the total number of trials chosen can be based on the variability that you find during the equipment installation qualification.

Process Performance Qualification

Once the equipment installation qualification has been completed succesfully, you are ready to proced with the next

stage of validation, performance qualification. The FDA validation guideline defines this as follows: process performance qualification- establishing confidence that the process is effective and reproducible.

At this point, you should have already worked out the manufacturing process in the pilot laboratory and been assured that it is ready for scale-up to production equipment. Each stage in the process should be defined in writing so that the employees who will actually operate the equipment know what is required of them. These written procedures can form the basis for batch production and control records after the process is finalized.

Here again, the << WORST CASE >> challenge should be used, keeping in mind that the conditions should simulate those expected during actual production. For a high speed tabletting machine, you would not want to run it so fast that the punches and dies collide! however, you would want to run it at the maximum safe speed comparable with the flow characteristics for that particular granulation.

The guideline gives an example of what can happen when changing from one type of granulation blender to another without altering the mixing times or procedures. If the blenders are substantially different, it could result in a granulation with poor distribution of ingredients. Also in blending of drugs that are potent in low doses, beware of raw materials which may agglomerate. FDA is aware of situations where tiny agglomerates may combine with a disproportionately large amount of the active ingredient. These physical properties could result in the amount of active ingredient present in a single tablet being doubled. In the granulation, the amount of moisture present may be a critical factor. With some tablets, dissolution time can be affected by the variance in the amount of moisure in the granulation. Often, this type of variance does not show up until the tablets have aged somewhat.

Along the lines of reproducibility, we want to look at the tableting machine itself. Samples of the tablets should be taken

at various times throughout the run and subjected to individual tablet assays. You may find variability with single tablet assays depending on a number of factors. In the past, FDA has found a variation between the beginning or end of the run compared with the middle of the run by as much as 25 % of the declared potency! controls that are carried out during the course of the processing can be of major importance in validating tablet manufacture. While the full range of tests and assays carried out in the analytical laboratory after production are also important, those in-process tests are critical. They alert the operator to adjust the machine if needed to bring the operation back within the tentative upper and lower control-range limits. If in-process sampling and testing is carried out conscientiously, it can be a major in assuring that the run is will remain well within the targetted range of the process validation.

Batch records were noted earlier in regard to the need for employees to know what is required of them. FDA has found a few areas of weakness in batch production records. One is the lack of specific information such as the order of blending of the ingredients. This can have a critical effect on the outcome of the batch, particularly when you have drugs that are potent in low doses. Another point to rememder is that the batch record should specify which piece of equipment should be used. This desicion cannot be left to an operator any longer. With a validated process, it is not acceptable to merely direct an operator, on a batch record, to use a << suitable mixer >>. Each specific piece of equipment must be listed.

One of the last stages in the production and control of tablets is the submission of samples to the laboratory for a comprehensive battery of physical and chemical tests. The FDA guideline addresses validation in regard to tablets in six areas. They single out tablet size, weight, hardness and freedom from defects, as well as potency of those tablets and bioavailability. For bioavailability, we find that it is often related to the disingtegration and dissolution properties of the tablets. Each

manufacturer will want to make sure that they known as much as possible about variables in these areas.

For final testing, as part of validation studies on tablets, one of the most important areas appears in the USP (and other world pharmacopiea) under the title of uniformity of dosage units. Previously, the USP had two separate sections. one on tablet weight variation and another on centent uniformity. The approach has been changed from checking weight variaiton to conducting individual tablet assays for content uniformity. New emphasis has been placed on statistical evaluation of the content uniformity test results, the relative standard deviation. While results of the individual tablet assays are allowed to vary as much as plus or minus 15% of the potency on the label, the croupings of the tablet assasys as a whole must be tighter. The USP specifies a maximum of 6% relative standard deviation for the first en individual tablet assays. If the first ten individual tablets assayed are found outside of the 6% range, an additional 20 tablets have to be tested. The range for the accumulated total of 30 tablets cannot exceed 7.8% for relative standard deviation.

The results of all analytical testing should be watched in a trend monitoring procedure. Repeated failure of certain analytical tests should be an alert that the process validation may not be adequate. This would include repeated failures in the area of potency testing, uniformity or dissolution testing. One other factor that can cause variability in laboratory results is the procedure of reworking of the batch. FDA has found instances where the reworking has affected the bioavailability of the drug product.

Documentation of the validation program is an essential step in making sure that the process is adequately controlled. As we noted earlier, you will want to review all of the data gathered in the validation procedure and record the details of each process. The format of the documentation is important in that the data should be analyzed and then summarized in a very concise manner. You should write conslusions based on your validation

procedures as to whether or not you consider the process to be validated. The basis for your conclusion should also be distinctly noted in the summary.

Certification is the last stage in the validation procedure. By this I refer to certificaiton by management of the accuracy and completeness of the data which has been accumulated on each product. In general, it is desirable that the signatures of upper management appear on the document to certify its accuracy,

CONCLUSION

To summarize process performance, define each process as accurately as possible and then establish an acceptable range for that process. Challenge any aspect that could cause a variation while staying close to the actual conditions under which the product will be manufactured.

You should also establish criteria for those changes in the process that are sufficiently significant to require revalidation. These would include changes in formulation or equipment or new packaging. As we noted earlier, change of a raw material supplier may initiate revalidation.

To be sure that revalidation is carried out when necessary, designate a person to be responsible for reviewing changes in products, processes, equipment and personnel.

Revalidation of the entire process is not always necessary depending on where the changes are made. However, carefully consider how the changed aspect will interact with other operations before a final decision is made.

While validation of a drug manufacturing process is required by the United States Food and Drug Administration, it also happens to be << GOOD BUSINESS >>. By avoiding just one product market recall, validation can pay for itself.