Drug Information Journal, Vol. 31, pp. 1195–1201, 1997
Printed in the USA.
0092-8615/97

PHARMACEUTICAL VALIDATION AND PROCESS CONTROLS IN DRUG DEVELOPMENT

SHEIN-CHUNG CHOW, PHD
Executive Director, Biostatistics and Data Management, Covance, Inc., Princeton, New Jersey

In drug development, pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity, and stability of the drug product. Pharmaceutical validation includes analytical method validation and (manufacturing) process validation. A validated analytical method is often employed for product testing at various critical stages of a manufacturing process to evaluate whether the manufacturing process does what it purports to do. For a validated manufacturing process, the current good manufacturing practice requires that a well-written procedure for process controls be established to monitor the performance of the manufacturing process. In this paper, statistical issues and regulatory requirements for pharmaceutical validation and process controls in drug development are discussed. The concept can be applied to new drugs, new dosage forms, and generic drug development.

Key Words: Assay validation; Process validation; Quality assurance; United States pharmacopeia tests; Release targets

INTRODUCTION

THE DEVELOPMENT OF A drug product is a lengthy process which involves drug discovery, laboratory testing, animal studies, clinical trials, and regulatory registration. This lengthy process is necessary to ensure the effectiveness and safety of the drug product. After the drug is approved, most regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity, and stability before it can be released for use. For this purpose, pharmaceutical validation and process controls are important to assure that the drug product at various stages of drug development can meet standards for the identity, strength, quality, purity, and stability of the drug product. Note that the standards are usually referred to as the standards specified in the United States Pharmacopeia and National Formulary (USP/NF) (1).

Pharmaceutical validation includes the validation of laboratory instruments such as gas chromatography (GC) and high-performance liquid chromatography (HPLC) or analytical methods developed based on these instruments and manufacturing processes for specific compounds. The current good manufacturing practice (cGMP) requires that the sponsors establish the reliability of test results through appropriate validation of the test results at appropriate intervals (21 CFR 210 and 211). More specifically, the cGMP requires that the accuracy and reliability of

Presented at the DIA "First International Taipei Symposium," August 29–30, 1996, Taipei, Taiwan.

Reprint address: Shein-Chung Chow, PhD, Biostatistics and Data Management, Covance, Inc., Princeton, NJ 08540.

test results be established and validated. The purpose of analytical method validation is then to ensure that the assay result meets proper standards of accuracy and reliability, while the purpose of the manufacturing process is to ensure that the manufacturing process does what it purports to do. Therefore, a validated analytical method is usually employed for product testing at various critical stages of a manufacturing process to evaluate whether the manufacturing process does what it purports to do.

After a manufacturing process is validated, the current good manufacturing practice also requires that a well-written procedure for process controls be established to monitor the performance of the manufacturing process. Process controls include raw materials inspection, in-process controls, and release targets for final product. The purpose of process controls is to monitor the on-line and off-line performance of the manufacturing process and consequently validate the manufacturing process.

This paper provides an overview of pharmaceutical validation and process controls in drug development. The concept can be applied to new drugs, new dosage forms, and generic drug development. In addition, some statistical issues and regulatory requirements for pharmaceutical validation and process controls in drug development are discussed.

PHARMACEUTICAL VALIDATION

Assay Validation

When a new pharmaceutical compound is discovered, the FDA requires that an analytical method or test procedure for determination of the active ingredients of the compound be developed and validated before it can be applied to animal and/or human subjects. As indicated earlier, the cGMP requires that test methods, which are used for assessing compliance of pharmaceutical products with established specifications, must meet proper standards of accuracy and reliability. The General Chapter 1225 of the USP/NF defines the validation of analytical methods as the process by which it is established, in laboratory studies, that performance characteristics of the methods meet the requirements for the intended analytical application.

The analytical application may be referred to as a drug potency assay which is usually based on GC or HPLC for potency and stability studies, immunoassays such as radioimmunoassay (RIA) for the *in vitro* activity of an antibody or antigen, or a biological assay for the *in vivo* activity such as median effective dose (ED_{50}). The performance characteristics include accuracy, precision, limit of detection, limit of quantitation, selectivity (or specificity), linearity, range, and ruggedness which are useful measures for assessment of accuracy and reliability of the assay results. Among these performance characteristics, accuracy, precision, and ruggedness are considered the primary parameters for the validation of an analytical method.

For the validation of an analytical method, whether the analytical method can generate true values is often of great concern. To address this question, one may measure how close the assay result obtained by the analytical method is to the true value. This performance characteristic is referred to as the accuracy of the assay result. In practice, one may consider the analytical method to be validated in terms of accuracy if the mean value is within ±15% of the actual value, except at the limit of quantitation (LOQ), where it should not deviate by more than 20% (2). In addition, the precision which is defined as the degree of agreement among individual assay results when the assay method is applied repeatedly to multiple sampling of a homogeneous sample can be measured based on measurement error of the assay. Similarly, Shah et al. (2) indicated that one may claim that the analytical method is validated if the precision around the mean value does not exceed a 15% coefficient of variation (CV), except for LOQ, where it should not exceed 20% CV.

In many cases, the analytical method may be performed by different analysts and different laboratories under different operating cir-

cumstances such as different instruments, different lots of reagents, different elapse time, or different assay temperatures. Assay ruggedness is often used to assess the influence of uncontrollable factors or the degree of reproducibility on assay performance. One may conclude that the analytical method is validated in terms of reproducibility if its assay ruggedness is within 15% of the mean value.

Accuracy is typically assessed using multiple testing by linear regression (3,4). Precision can be assessed by testing hypothesis of variability less than an acceptable limit. Typical approaches for assessing assay ruggedness include the one-way nested random effects model and the two-way crossed-classification mixed model (5). For the assessment of assay ruggedness, it should be noted, however, that the classical analysis of variance method may produce negative estimates for the variance components and that the sum of best estimates of variance components may not be the best estimate of the total variability. In these situations, methods proposed by Chow and Shao (6) and Chow and Tse (7) may be useful.

In practice, the validation of an analytical method can be carried out by the following steps:

1. It is important to develop a prospective protocol which clearly states the validation design, sampling procedure, acceptance criteria for the performance characteristics to be evaluated, and how the validation is to be carried out,
2. Collect the data and document the experiment, including any violations from the protocol that may occur. The data should be audited to assure their quality. The collected data are then analyzed based on appropriate statistical methods. Appropriate statistical methods are referred to as those methods which can reflect the validation design and meet the study objective, and
3. Draw a conclusion regarding whether the analytical method is validated based on the statistical inference drawn about the accuracy, precision, and ruggedness of the assay results.

Process Validation

The objective of the validation of a manufacturing process is to ensure that the manufacturing process does what it purports to do. A validated process assures that the final product has a high probability of meeting the standards for identity, strength, quality, purity, and stability of the drug product. A manufacturing process is a continuous process which usually involves a number of critical stages. For example, for the manufacturing of tablets, the process may include initial blending, mill, primary blending, final blending, compression, and coating stages. At each critical stage, some problems may occur. For example, the ingredients may not be uniformly mixed at the primary blending stage; the segregation may occur at the final blending stage, and the weight of tablets may not be suitably controlled during the compression stage. In practice, therefore, it is important to evaluate the performance of the manufacturing at each critical stage by testing in-process and/or processed materials for potency, dosage uniformity, dissolution, and disintegration according to sampling plans and acceptance criteria stated in the USP/NF. These tests are usually referred to as the USP tests. For sampling plans of USP tests, the USP/NF requires that representative samples be drawn from the container.

A manufacturing process is considered to pass the USP/NF tests if each critical stage of the manufacturing process and the final product meet the required USP/NF specifications for the identity, strength, quality, and purity of the drug product. A manufacturing process is considered validated if at least three validation batches (or lots) pass all required USP/NF tests. Since manufacturing procedures vary from drug product to drug product and/or from site to site during the development of a validation protocol of a manufacturing process, it is important to discuss the issues given in Table 1 with project

TABLE 1
Practical Issues in Process Validation

Critical stages
Equipment to be used at each critical stage
Possible problems
USP tests to be performed
Sampling plans
Testing plans
Acceptance criteria
Pertinent information
Test or specification to be used as reference
Validation summary

scientists to acquire a good understanding of the manufacturing process.

Process validation usually refers to the establishment of documented evidence that a process does what it purports to do (8). Basically, there are four different types of manufacturing process validations in the pharmaceutical industry: prospective, concurrent, and retrospective validations, and revalidation. Prospective validation establishes documented evidence that a process does what it purports to do based on a preplanned protocol. Prospective validation is usually performed in the situations where:

1. Historical data are not available or sufficient and in-process and end-product testing data are not adequate,
2. New equipment or components are used,
3. A new product is reformulated from an existing product, or there are significant modifications or changes in the manufacturing process, and
4. The manufacturing process is transferred from development laboratory to full-scale production.

Retrospective validation provides documented evidence based on review and analysis of historical information which is useful when there is a stable process with a large historical database. One of the objectives of the retrospective validation is to support the confidence of the process. Concurrent validation evaluates the process based on information generated during actual implementation of the process. In some situations where:

1. A step of the process is modified,
2. The product is made infrequently, and
3. A new raw material must be introduced,

a concurrent validation is recommended.

In practice, a well established manufacturing process may need to be revalidated when there are changes in critical components (eg, raw materials), changes/replacement of equipment, changes in facility/plant (eg, location or size), and a significant increase and/or decrease in batch size.

For a validated process, there is no guarantee that if the test is performed again it will have a high probability of meeting the specification. Thus, it is of interest to construct some in-house acceptance limits (specifications) which guarantee that future batches produced by the process will pass the USP test with a high probability. A common approach to process validation is to obtain a single sample and test the attributes of interest to see whether the USP/NF specifications are met. Bergum (9) proposed constructing acceptance limits that guarantee that future samples from a batch will meet a given product specification a given percentage of times. The idea is to consider a multiple stage test. If the criteria for the first stage are met, the test is passed. If the criteria for the first stage are not met, then additional stages of testing are done. If the criteria at any stage are met, the test is passed. Acceptance limits for a validation sample are then constructed based on sample mean and standard deviation of the test results to assure that a future sample will have at least a certain chance of passing a multiple stage test. More details can be found in Chow and Liu (5).

PROCESS CONTROLS

For monitoring the performance of the manufacturing process, cGMP requires that a well-written procedure for process controls be established and followed. The process controls should be examined based on representative samples drawn from each batch according to sampling plans as specified in cGMP or USP/NF. The objective of process controls is to

control expected and/or unexpected sources of variabilities that may occur during the manufacturing process. When there is a deviation from established control specifications, the possible causes for the deviation must be found and immediate corrective actions must be taken. Process controls are usually referred to as raw material inspection, in-process materials quality assurance, and final product quality control and release targets.

Raw Material Inspection

Quality assurance generally starts with raw materials inspection. The objective of raw materials inspection is to examine whether the raw materials meet USP/NF specifications for the identity, strength, quality, and purity of the drug product. Unacceptable raw materials can certainly lead to unacceptable products. Therefore, it is crucial to inspect all of the raw materials to make sure that they meet USP/NF standards for the identity, strength, quality, and purity of the drug product before the manufacturing process is initiated. For the inspection of raw materials, the quality control unit usually performs USP tests for drug characteristics such as potency based on samples drawn from the raw materials that are usually stored in drums. Based on the test results, the quality control unit can determine whether the raw materials should be approved for future use or be rejected. Once the raw materials pass the inspection, they can be used for manufacturing.

Since the raw materials are usually stored in drums, a two-stage sampling technique is usually performed to draw representative samples for inspection. For the first stage of sampling, one selects a number of drums at random. A conventional ad hoc approach is to select the square of the total number of drums. This method is easy to apply, however, it does not have any scientific and/or statistical justification. For each sampled drum, cGMP suggests that random samples be drawn from the top, middle, and bottom parts of the drum with a grain thief, which consists of three compartments. Based on the test results, the quality control unit is able to determine whether the raw materials pass the inspection.

In practice, the strengths of the raw materials stored in the drums, which had passed quality control inspection, may differ from drum to drum due to the possible segregation of the materials. Thus, prior to manufacturing, it is important to determine the amount of materials to be used for mixing from each drum so that the mixed raw materials will achieve the desired strength. Since each drum may have a different volume of materials, however, it is a challenge for the quality control unit to select the right number of drums and the corresponding right volumes of materials for mixing so the capacity of the V-blender is fully utilized and the mixed raw materials will achieve the targeted strength (5). To assure that the mixed raw materials will achieve the targeted strength, the quality control unit usually establishes quality assurance limits to accept or reject the mixed materials.

In-process Controls

At each stage of the manufacturing process, the in-process materials including any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in preparation of, the drug product should be tested to control the expected and unexpected sources of variations. Therefore, the objective of in-process controls is not only to detect/identify the possible cause of any unusual fluctuations in a process, but also to locate/correct the problems where the unusual fluctuations occur. Since the manufacturing process of a drug product is a continuous process, the characteristics of the drug product may fluctuate from time to time at each critical stage of the process. Some fluctuations may be explained by the inherent variability of the process. Other fluctuations may be due to variation from identifiable sources. The responsibility of the quality control unit is then to remove identifiable sources of variations.

During the manufacturing process, statistical control charts such as Shewhart control

charts (eg, $\overline{X}$, R and $\overline{P}$ charts), acceptance control charts, and cumulative sum control charts are often employed as useful graphical devices to monitor whether the variabilities of the drug characteristics are within acceptable limits (10,11,12). The basic idea of Shewhart control charts is first to remove any assignable causes of variation whenever possible based on an estimated short-term variability. After the assignable causes of variation have been identified and removed, the estimated variability can be used to establish control limits for evaluation of long-term variability. To ensure that the manufacturing process will reach the state of statistical control, it is recommended that the sample mean and sample range be used to capture any changes in location and variability in the control charts.

An acceptable control chart is developed based on the concept that the drug characteristics can be classified as either at an acceptable process level (APL) or a rejectable process level (RPL). Therefore, APL (RPL) is a process level at which it is acceptable (rejectable) and should be accepted (rejected) most of the time. Hence, an acceptable control chart can be used to determine whether a process should be accepted or rejected based on whether the drug product meets USP/NF specifications. Note that acceptance control charts are usually applied when the variability of a process is stable and in a state of statistical control. In practice, acceptance control charts are generally used in conjunction with a Shewhart control chart to ensure the stability of the process in terms of its process variability.

Since Shewhart control charts are based on a one-point rule which declares that a process is out of the state of statistical control if the last sample mean is beyond the control limit, they are not efficient in identifying small-to-moderate deviations. To overcome this drawback, Page (12) developed a procedure for control charts based on the sum of observations. Each point on this type of control charts contains information on all previous points including itself. This control chart is known as cumulative sum (CUSUM) control chart which utilizes all cumulative historical data up to the present time to detect any changes rapidly.

Release Targets

The objective of release targets is to determine whether a batch or lot of a drug product can be released for use based on USP tests. A common approach to release testing is to obtain a single sample and test the drug characteristic of interest. If the specification for the tested characteristic is met, the batch is released. For each test, the quality control unit may construct acceptance limits based on other experiments such as assay validation or stability studies. These acceptance limits are usually referred to as release targets. The constructed release targets guarantee that future samples from a batch meet a given product specification a given percentage of times.

As an example, consider release testing for potency. The USP/NF requires that the average potency of a batch be within an interval (L,U), where $0 < L < U$ represent USP/NF specification limits. Since the average potency is unknown, the release test is based on a potency assay result of a sample or the average potency results of n samples from the batch. A batch might be released if its potency assay result is within (L,U). A batch released according to such a test criterion, however, could have average potency outside (L,U) with a high probability. A batch having average potency outside the USP/NF specifications before the expiration dating period is subject to recall. To have a certain degree of assurance that the average potency of a batch is within (L,U), the quality control unit usually selects in-house release targets (a,b) as a guide for releasing a batch. As a result, a is chosen to be $L + 1.645\hat{\sigma} + \hat{s}$ and b is selected as $U - 1.645\hat{\sigma}$, where $\hat{\sigma}$ is the estimated variability of an assay and $\hat{s}$ is the estimated stability loss in potency over the entire expiration period. The idea behind this set of release targets is that if all future batches have the same average potency, release targets guarantee that among all the

future batches released, 90% have average potency within (L,U).

As an alternative, Shao and Chow (13) proposed a Bayesian decision theory approach to construct release targets for drug characteristics such as potency and dissolution by minimizing the expected loss (or maximizing the expected gain).

CONCLUSIONS

In new drug research and development, before a drug can be approved, the sponsors are required to demonstrate its effectiveness and safety for the intended indication and target patient population. To provide an accurate and reliable assessment, pharmaceutical validation such as assay validation plays an important role. For example, assay validation is crucial in stability analyses, animal studies, and early phases of clinical development such as bioavailability/bioequivalence studies. After the drug is approved, pharmaceutical validations and process controls are necessary to ensure that the drug product will meet the USP/NF standards for the identity, strength, quality, purity, and stability of the drug product for evaluation of safety and efficacy of drug products.

Assay validation assures the accuracy and reliability of test results for drug identity, strength, quality, and purity according to the USP/NF standards. Process validation guarantees the reliability and reproducibility of the manufacturing process. Process controls control expected and/or unexpected sources of variabilities that may occur during the manufacturing process. In conclusion, pharmaceutical validation and process controls provide a certain assurance of batch uniformity and integrity of the drug product manufactured. To achieve this objective, it is strongly suggested that appropriate statistical design and analysis be employed to establish pharmaceutical validation and process controls whenever possible.

REFERENCES

1. USP/NF. The United States Pharmacopeia XXIII and the National Formulary XVIII. Rockville, MD: The United States Pharmacopoeial Convention, Inc.; 1995.
2. Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A, Layloff T, Viswanathan CT, Cook CE, McDowall RD, Pittman KA, Spector S. Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. *J Pharm Sci.* 1992;81: 309–312.
3. Bohidar NR. Statistical aspects of chemical assay validation. Proceedings of the Biopharmaceutical Section of the American Statistical Association; 1983:57–62.
4. Kohberger RC. Manufacturing and quality control. Chapter 4 in *Biopharmaceutical Statistics for Drug Development*. Peace, KE, Ed. New York: Marcel Dekker, Inc.; 1988:605–629.
5. Chow SC, Liu JP. *Statistical Design and Analysis in Pharmaceutical Science*. New York: Marcel Dekker, Inc.; 1995.
6. Chow SC, Shao J. A new procedure for the estimation of variance components. *Stat & Prob Lett*. 1988; 6:349–355.
7. Chow SC, Tse SK. On variance estimation in assay validation. *Stat Med*. 1991;10:1543–1553.
8. Chapman K. A suggested validation. *Lexicon Pharm Tech*. 1983;7:51–57.
9. Bergum JS. Constructing acceptance limits for multiple stage tests. *Drug Develop Indul Pharma.* 1990; 16:2153–2166.
10. Shewhart WA. *Economic Control of Quality of Manufactured Product*. New York: D. Van Nostrand; 1931.
11. Freund RA. Acceptance control charts. *Ind Qual Cont.* 1957;14:13–23.
12. Page ES. Continuous inspection schemes. *Biometrika*. 1954;41:100–115.
13. Shao J, Chow SC. Constructing release targets for drug products: a decision theory approach. *J Roy Stat Soc, C.* 1991;40:381–390.