Quality Engineering, 4(4), 649–657 (1992)

STATISTICAL QUALITY CONTROL IN THE MANUFACTURE OF PHARMACEUTICALS

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Purpose

There have been many attempts to define briefly the phrase "quality control by statistical methods." Most brief definitions do not indicate much more information than the phrase itself, and as the literature on the industrial applications of statistical methodology becomes more voluminous, it is increasingly apparent that a definition that will be broad enough to include the entire area of application and at the same time specific enough to give adequate meaning, has little chance of ever being written.

The absence of an adequate definition for a subject, however, does not preclude a description of some of its salient features and a discussion of what it can and has accomplished when applied to industrial problems. Therefore, the purpose of this paper is to present some basic concepts of statistical quality control and to enumerate some of the things that can be expected from it when it is applied in the right proportion with other technology to some of the problems of the pharmaceutical industry, and to give illustrative examples as space permits.

SQC and Pharmaceutical Practice

The fundamental concept of statistical quality control and the fundamental concept, "good pharmaceutical practice," are one and the same thing. It is the basic idea of building quality into a product by maintaining a rigid set of manufacturing controls on every step of the production process. Our industry has developed this idea by employing manufacturing control systems that, by and large, are far more comprehensive than the systems utilized by most other industries. In fact, the basic philosophy of statistical quality control is so like that of pharmaceutical quality control that it is surprising that our industry was not the first to adopt it.

To build quality into a product may well be the sincere desire of every worker in the plant but how to accomplish this economically is still another matter. It must be obvious that one of the necessary tools for accomplishing this feat is one which will provide a factual basis for evaluating a production process and which will enable specifications to be set in a scientific manner. Statistical quality control is a tool which meets these requirements. It does so by applying the relatively simple mathematics of nature to problems in which there is a strong tendency toward arbitrary decisions and thus it eliminates the errors arising from guess work.

Statistical quality control recognizes one principle that is at times difficult for the pharmaceutical manufacturer to digest. This is the principle of variation. Statistical quality control accepts the fact that no two manufactured products are exactly alike regardless of the refinements made in the production process. It also recognizes that there usually is a large number of causes which contribute to the total variation between individual units of the same product, but, unlike other methods, it provides factual evidence which will discriminate between those variations that can be identified with an assignable cause and those which are naturally inherent in the specific process. In addition, the fundamental techniques of the method are practical enough to be applied routinely by operating personnel without any excessive additional supervision.

The common practice in setting quality levels in the pharmaceutical industry seems to follow a pattern of establishing, as a minimum, the standards of the official compendia and then adding a certain "plus value" which represents the quality standards of the individual management. There is nothing wrong with such a practice but it should be pointed out that the administration of this policy is beset with pitfalls which must be avoided if the enterprise is to be successful. There is always the danger of allowing such a practice to give birth to noncompetitive quality standards. This can happen in one of two ways both of which produce equally serious consequences. First, quality levels can be raised to heights that will quickly destroy the competitive cost structure. Secondly, they can be lowered to levels that will involve the producer in excessive risks from both the

market and legal standpoints. Clearly then, some middle of the road policy must be adopted and this is no easy task for the road is, most generally, a narrow one and expert driving will be required.

How SQC Can Help

What can statistical quality control do to help solve this problem? Before this question is answered, it should be emphasized that the method has been referred to elsewhere in this paper as only a tool and it should be understood that it is not a panacea for all of the problems of the industry. Nevertheless, some of the things we can expect of it in helping to solve the problem at hand can be enumerated.

First, we can expect its use to affect economies in the use of raw materials by providing a basis for more realistic specifications for purchased goods and better scientific sampling methods for incoming materials. Economies in raw materials are also indirectly effected through a more efficient utilization of them as a result of process control.

Second, it can be expected that economies in the use of both man and machine power will be realized. Usually this is accomplished by an increase in output per man-hour and per machine-hour, which is the net result of putting man power to work on the investigation of variations that are identified with some assignable cause rather than wasting man power in a guessing game on where the trouble may be. It also stems from a reduction in the number of reoperations required.

Third, statistical quality control can be expected to reduce inspection costs. This is accomplished by substituting process inspection for product inspection and utilizing scientific sampling plans for check inspection of the final product.

Fourth, in-process control by this method can be expected to reduce the production of rejects.

Fifth, the acceptance of this method of in-process control improves the relationship between the production and control groups because the method provides objective records which supplant subjective opinions.

Sixth, the control department has a charted record, which, carefully read, provides a quick history of the progress of a particular lot through the production process. In case of any doubtful results in the official tests, appeal to the chart allows the control department to evaluate the seriousness of such results and make decisions concerning the lot which are more meaningful than the usual arbitrary rejection or acceptance. Production quickly learns that the chart is its best friend and not an additional club of the control department.

Finally, management can be assured of an improved quality level and more homogeneous product produced at lower costs. Also, the method will provide management with discriminating information concerning quality levels which they otherwise seldom get.

Setting Realistic Specifications by Statistical Analysis

So much for the point of view and a broad outline of the features of statistical quality control. At this point, let us shift from the general to the particular by considering in some detail an application of these principles to a manufacturing process.

Consider the problem of controlling the filling of a relatively viscous injectable suspension in multiple dose containers. The specification reads that ten separate 1 cc injections shall be available from a 10-dose vial. The overall problem is simply how much must be put into the vial to meet this specification. It has already been intimated that there are those who would recommend putting in an *adequate* amount. This is highly laudable but not feasible under today's condition of competition. The proper procedure is to find the *right* amount to fill into these vials.

The first step is to catalog the sources of variability in both the filling and the testing. In this case they are:

1. The residual amount of material in the syringe and the variability between syringes—syringe holdup.
2. The residual amount of material which cannot be withdrawn from the vial and the variability in this amount from vial to vial—vial holdup.
3. The specific gravity of the suspension and its variability from lot to lot.
4. The variability of the filling equipment.

The average value for each of these contributing sources of variability and a measure of the dispersion about it can be easily and quickly obtained. This is done by making several measurements (preferably 20 or more) of the syringe holdup, vial holdup, etc. and calculating the average value for each. The measure of dispersion is obtained by calculating the standard deviation (σ') which is given by

$$\sigma' = \sqrt{\frac{\Sigma X^2 - (\Sigma X)^2/N}{N - 1}}$$

where X is equal to an individual measurement, Σ denotes summation, and N is equal to the number of measurements in the series. The square of this value is known as the variance.

The averages and standard deviations are shown in Table 1.

The variability in specific gravity from lot to lot was small and well within the variability associated with several determinations on the same lot of material and, therefore, its contribution was insignificant. Having these values available, it is now possible to calculate what the filling figure should be. It was desired that this be in terms of weight, and thus the filling figure is derived from the following formula:

$$(10.0)(1.007) + 0.506 + (10.0)(0.150) \pm 3\sqrt{\sigma^2 s + \sigma^2 v + \sigma^2_F}.$$

Table 1.

SOURCE	AVERAGE	STANDARD DEVIATION
Syringe holdup (1 cc dose)	0.150 g	0.0052 g = σ_s
Vial holdup (10 cc vial)	0.506 g	0.0430 g = σ_v
Specific gravity	1.007	Nil
Variation in filling equipment	10.00 cc	0.034 g = σ_F

This formula converts 10 cc to grams by multiplying by the average specific gravity and adds the average vial holdup in grams, the average syringe holdup in grams, and finally takes into account three times the square root of the sum of the contributing variances in grams, viz:

$$(10.0)(1.007) + 0.506 + (10.0)(0.150) \pm 3\sqrt{0.0052^2 + 0.043^2 + 0.034^2}$$

$$= \begin{cases} 12.241 \\ 11.911 \end{cases}$$

The reason for including three times the square root of the sum of the variances can be explained best by the diagram shown in Figure 1. In terms of weight, 10.07 g must be averagely obtained for ten 1 cc injections. The vial holdup will be on average 0.506 g and the holdup in the syringe is on average 0.15 g/cc or 1.5 g for 10 cc. These total an amount equal to 12.076 g. The individual values, however, which made up the respective averages vary about them according to the normal or Gaussian curve and it is possible to calculate a value about each of these separate averages which will include about 99.73% of the individual values making up the average. This is done by adding and subtracting from each average an amount equal to three times the standard deviation for the respective measurements. However, the distribution of the sum of N normal and independent variables each of normal form also produces a normal or Gaussian curve whose standard deviation is equal to the square root of the sum of the individual standard deviations squared (variances). In this example, the square root of the sum of the variances was 0.055 g. This is the total standard deviation (σ_t) and $3\sigma_t = 0.165$ g (Fig. 1).

When the filling machines are set to deliver an average of 12.241 g (Fig. 1), one can expect about 99.73% of the vials to contain between 12.076 g and 12.406 g, respectively. That is, there is a chance that approximately 3 out of 1000 vials will contain a quantity outside of these ranges; and further since the curve is symmetrical, the chances are equal (0.00135) that a vial will exceed the upper or lower limit, respectively. Thus, the probability of distributing into the trade an underfilled vial is 0.00135.

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