17 Quality by Design

INTRODUCTION

It has long been a principle of scientific discovery that a rational strategy is essential to a clear understanding of phenomena and to the creation of knowledge. Engineering processes present a level of complexity with respect to operating variables that contribute to their efficiency and reproducibility and challenge the ability to design experiments sufficiently robust to probe the range of operating conditions to identify optimal parameters.

The approach to statistical experimental design will be described in the next chapter (chap. 18). Several higher-level considerations will be outlined in the following discussion to allow sufficient definition of any process before it is subjected to experimental evaluation.

REGULATORY INITIATIVE

In recent years several regulatory agencies have indicated their desire to have Quality by Design tools adopted to justify the various processes employed in the production of a pharmaceutical product to manage risk associated with the quality of the product. Notable among these are the guidances of the U.S. Food and Drug Administration and the relevant guidances (Q8–10) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Figure 17.1 depicts the relationships beween the ICH quality chapters and their intent to (*i*) use quality systems, such as process analytical technology or measurement and control of operating variables, in (*ii*) risk analyses, which establishes priority of these measurements through (*iii*) statistically designed experiments in product development that identifies variable parameters and acceptable variances with respect to measured and monitored phenomena.

Consideration of each of these items allows process space to be defined. That is the range of input variable control that is required to minimally impact on the quality of the product and thereby ensure the uniformity and reproducibility of the final product derived from the various processes employed.

Quality by design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control on the basis of sound science and quality risk management (Pharmaceutical development Annex to ICH, Q8, 2007).

Quality by Design is

- scientific, risk-based, holistic and proactive approach to pharmaceutical development;
- deliberate design effort from product conception through commercialization; and
- full understanding of how product attributes and process relate to product performance.

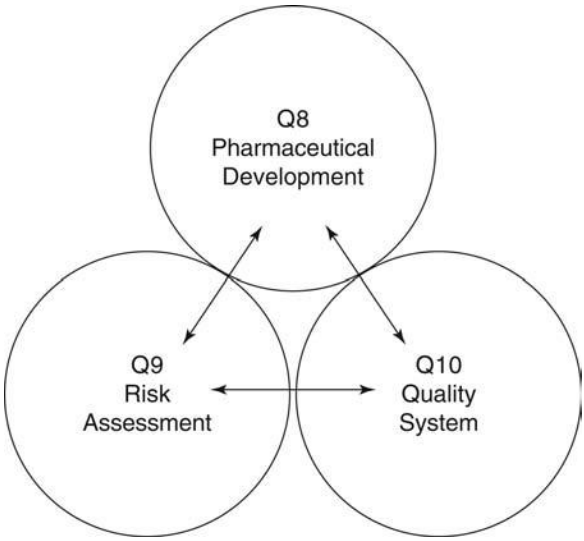

FIGURE 17.1 International Conference on Harmonization Quality by Design Guidances.

TOOLS FOR PROCESS DEVELOPMENT

Thorough documentation of all potential variables in a process is essential to defining the objectives of any experiments. It is rarely the case that a single individual has the capacity to create the database necessary to support this activity. Consequently, a variety of brainstorming tools intended to facilitate identification of all variables by a group of people involved in the process development have been designed. These include, but are not limited to, mind mapping and fishbone (Ishikawa) diagrams. It is important to use a tool that is most convenient and facilitates the thought process of the group. A mind map considers the way in which paths from an outer region of ignorance to a central well-defined process are characterized by the impinging variables as shown in Figure 17.2. A fishbone diagram defines a process as a linear phenomenon in which variable impinge on a line leading to a clearly defined output as shown in Figure 17.3. Depending on the stage of assessment and the intent of the review either of these approaches might be expected to give a thorough preliminary understanding of the process under consideration.

It is important to the process that all opinions are welcome, no judgment is placed on the priority of the input variable or that premature blocking (analysis) of the variables occurs. In this manner all parties who might be able to contribute to the discussion are encouraged and any dominant personalities are set aside for the purpose of the initial review. Only when all opinions have been rendered and a list of potential variables has been collected is the second step of blocking the variables, in terms of their dependency or their proximity, or distance from, the final output, undertaken. Again this should be reviewed by the group for general agreement on the framework of relationships of the variables under consideration.

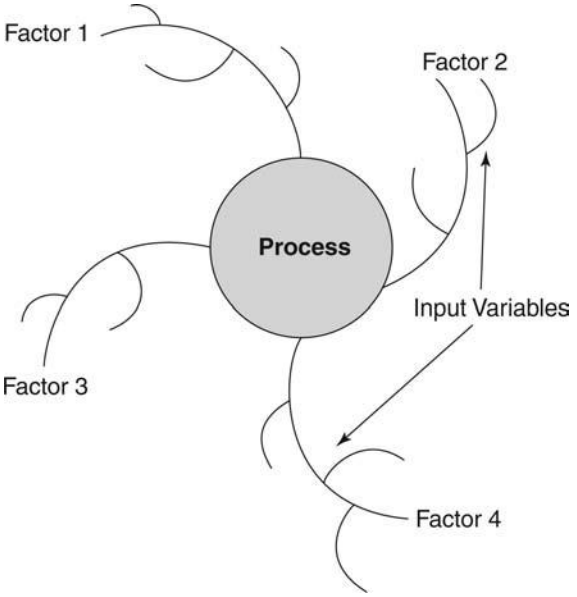

FIGURE 17.2 Schematic illustrating the approach to mind mapping.

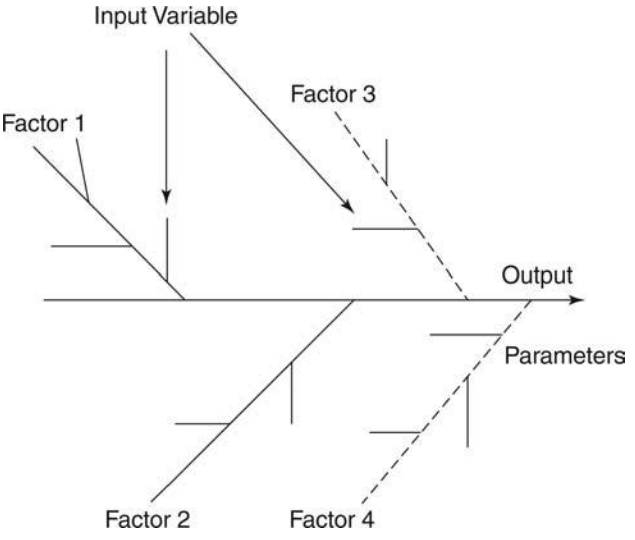

FIGURE 17.3 Schematic illustrating the fishbone approach to capturing input variables and their relationship to output properties.

Once a framework has been constructed, a judgment is made regarding the potential significance of each input variable to place emphasis in the experimental design on the potentially most significant variables. All minor variables are then controlled within defined limits to mitigate their contribution to the overall outcome of the subsequent experiments.

This approach has several valuable implications as follows for the process development:

1. It maximizes the potential of identifying all relevant variables.
2. It builds confidence in the group that all factors have been considered.
3. It allows a range of expertise to be brought to bear, which minimizes the potential to overlook factors.
4. Involves several opportunities to review and reevaluate before conducting time-consuming and sometimes expensive experiments.
5. Allows a rational experimental design that will lead to definition of process space.

To achieve these objectives appropriate statistical methods (chap. 18) and methods of obtaining data on the process are required, preferably with an ability for real-time monitoring and control through process analytical technology (chap. 19).

18 Statistical Experimental Design

INTRODUCTION

Statistical experimental design has been employed for optimization of complex multivariate processes central to pharmaceutical product development for several decades (Box et al., 1978; Cochran and Cox, 1957). The intent of experimental design is to rapidly and efficiently study many parameters to identify the combination of conditions that most efficiently and reproducibly generates a product with desired properties. These properties are most frequently uniform and reproducible drug delivery from a stable dosage form, but can extend to more subtle phenomena such as control of particular physicochemical properties or even cost and time efficiency of the process.

The general evolution of experimental design techniques begins with conventional randomized or Latin square approaches, factorial design and fractional factorial design, which yields significant and useful information with regard to the limits of input variables with respect to particular output properties. The results of these studies can be employed to identify regions of combinations of input parameters, so-called design space, that give rise to desirable output properties. Assessment by central composite experimental design yields more information regarding the curvature of design space, ultimately leading to complete response surface maps, which allow interpolation of changes in output as a continuous dependent function of the independent variable inputs. The following sections will describe each of these approaches in more detail. All lead to the concept of process design space, which leads to normal operating range from which product specifications can be developed.

Once input variables have been identified, according to the approach described in chapter 17, experiments can be designed that evaluate their contribution to the critical quality attributes of the product under development. Therefore, it is important to identify the output parameters and the techniques (see chap. 19) that will be employed to measure these properties to allow their response to the input variables to be characterized. Having considered these practical elements of the experimental design, the statistical approach has then to be selected for its relevance to the process under consideration.

SAMPLING

Before any experiments are conducted, the researcher must be aware of the limitations of sampling. The usefulness of any analytical method is based on the adequacy of sampling from the original population. Sampling techniques range in complexity from random methods through stratified sampling to spatial and adaptive sampling (Thompson, 2002). Sampling can be invasive, for example, thieves to remove samples from batches of powder blend, or noninvasive, as exemplified by laser optical techniques for particle sizing or spectroscopy, which are limited by the viewing volume usually dictated by the dimensions of the laser. The bias introduced by unrepresentative sampling can be sufficient to impair decisions and lead to erroneous conclusions about a

process. Consequently, representative sampling is a prerequisite to process analysis.

The use of statistics in quality control is not novel. Indeed the principles were established 70 years ago (Deming, 1938; Shewhart, 1939). These methods have since been incorporated into concepts of statistical process control (Oakland and Followell, 1986).

The basic principles of statistical analysis are beyond the scope of this volume and are the subject of a large number of foundational texts. In the realms of experimental design, Box, Hunter, and Hunter published the seminal text on "Statistics for Experimenters" in 1978. This remains a readable and informative text for those beginning to develop statistical tools to investigate processes with numerous variables.

Statistical methods mitigate the experimental difficulties associated with error (noise), confusion of correlation and causation, and complexity of the effects studied. There are many sources of experimental error that can be overcome with adequate experimental design and analysis. Frequently, examples of apparent correlations occur when two variable exhibit similar patterns that may exist because of their independent relationship to a third variable. Sound principles of experimental design, specifically randomization, provide a sound basis for deducing causation. Effects are sometime so complex that they do not conform to linearity or additive interpretation. Certain experimental designs allow for interactive and nonlinear effects to be estimated with little transmission of experimental error.

RANDOMIZED AND LATIN SQUARE DESIGNS

Allotting treatments to units by chance is the simplest layout of data for analysis. Specifically, if a treatment is to be applied to four units then randomization gives every group of four units in the experimental product an equal probability of receiving the treatment. The units should also be processed randomly at subsequent stages, where the order is likely to affect the results. For example, time of day, or season of the year, the samples are taken may influence processes that are susceptible to ambient conditions such as light, temperature, and humidity if these conditions are not controlled effectively. The advantages of this approach are complete flexibility, as any number of treatments and replicates may be employed, and ease of statistical analysis even if the numbers of replicates for some units or whole treatments are missing. Relative loss of information due to missing data is smaller than other designs. Criticism of this approach related to the loss of accuracy that occurs as a result of the whole variation is uniformly distributed across treatments and units and enters into the experimental error. The error can be reduced by use of different designs. The error can be reduced by introducing randomized blocks. The experimental product is divided into groups, each of which constitutes a single trial or replication. Using the example above, product could be blocked for time of day sample was taken to assign error specifically to ambient conditions.

For Latin square designs, treatments are grouped into replicates in two different ways. This approach effectively gives two dimensions to the analysis and the design assigns treatments to positions designated in a row or column of the design. Every row and every column of the square is a complete replication.

The effect of this double grouping is elimination from the errors all differences among rows and columns. Thus, the Latin square design provides more opportunity than random blocks for reduction of error by planning.

FACTORIAL DESIGN

The effects of a number of different factors are explored simultaneously in factorial designs. The treatment consists of all combinations that can be formed from the different factors. The simplest case is one in which each factor is considered at two levels. This is described as a 2^n factorial design. For example, a simple spray drying process requires consideration of input solution concentration and flow rate, airflow rate, and temperature, four factors. If each factor is studied at a high and low level, then this is described as a 2^4 factorial design.

The advantages of factorial experiments relate to their purpose. The intent is frequently to investigate the effects of each factor over some preassigned range that is covered by the levels of that factor, and not specifically to discover the combination of factors that results in the maximum or minimum response. Where the factors are independent, the statistical analysis is straightforward. However, where the factors are not independent there this additional information is to be gained through confounding analysis.

Factorial experiments are useful for exploratory experiments where the objective is rapid determination of the effects of a number of factors over a designated range; investigations of interactions among effects of several factors, all combinations of factors give the most information in this regard; experiments designed to lead to recommendations over a broad range of conditions. Where the objective is the latter recommendations, subsidiary factors may be brought into an experiment to test the principal factors under various conditions to those that are encountered in the population to which recommendations are to apply.

Fractional Factorial Design

Often full factorial designs are beyond the resources of the investigator, or the level of precision obtained is substantially higher than required. In a 2^6 factorial design, each main effect is an average of 32 combinations of other factors. It is possible that it would be sufficient to conduct a four- or eightfold replication and a partial experiment might be considered. Information is lost in this approach to experiments in particular with respect to interactions between factors.

There are hazards associated with this approach. The results of such experiments may be misinterpreted, particularly if the interactions that have been assumed to be negligible are not. The impact of this problem depends on decisions made from the results. In a screening study this may not have a huge impact where the implications for a fundamental research program could be very serious. In general, it is unadvisable to rely heavily on fractional factorial design as a tool for investigation unless the risk of being misled by the occurrence of factor interactions is considered small.

Central Composite Design

The designs above consider linear (first-order) relationships between levels of particular factors. However, the relationships between levels of factors may be related through nonlinear functions, the simplest of which is a quadratic

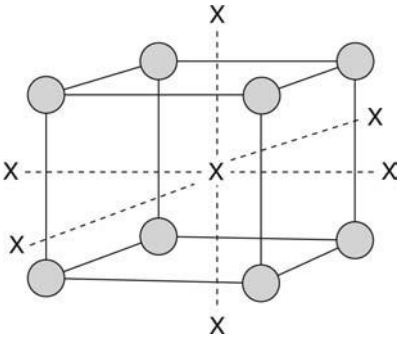

FIGURE 18.1 Central composite design (CCD) based on three factors (*x*, *y*, *z* axes). O, factorial design factor combinations; X, additional orthogonal factor combinations to complete the CCD.

response surface (second order) that can emerge from central composite designs (CCDs) based on factorial analysis. CCDs test additional factor combinations. CCD can be fitted into a sequential program of experimentation. The experiment starts with an exploratory 2^n factorial design to which a linear response surface is fitted. If the center of the first experiment is close to a point of maximum response, combinations of factors can be selected orthogonally to one of the original factorial designs to indicate the curvature of the response surface. Figure 18.1 illustrates the way factor combinations would be selected.

RESPONSE SURFACE MAPS

Extending the CCD model to a broad range of combinations of factors and levels allows for a continuous nonlinear surface to be plotted graphically that allows prediction of the response to variation in the factors (Myers and Montgomery, 1995). In the previous example, the response surface study begins when the process is near the optimum. At this point, it is desirable to accurately approximate the true response function within a small region around the optimum, recognizing that the true response exhibits curvature near this location. Sequential experiments are performed within some region of variable space identified as the operability region (OR). It is unlikely that the entire OR would be explored. Usually a region of interest (experimentation) around inflections in the OR will be investigated. The objectives of response surface methodology are generally mapping over a particular region of interest; optimization of the response; or selecting operating conditions to achieve specifications.

DESIGN SPACE

The distinction that can be made between a single response surface map and true process design space is that the latter is dynamic and begins when the drug is conceived and evolves over the entire life cycle of product (Fig. 18.2) (Lepore and Spavins, 2008).

The foregoing discussion was intended to outline the philosophy behind statistical approaches to experimental design and their relevance to pharmaceutical process optimization. The reader is referred to the texts cited and the broader foundational literature for thorough discussion of the mathematical

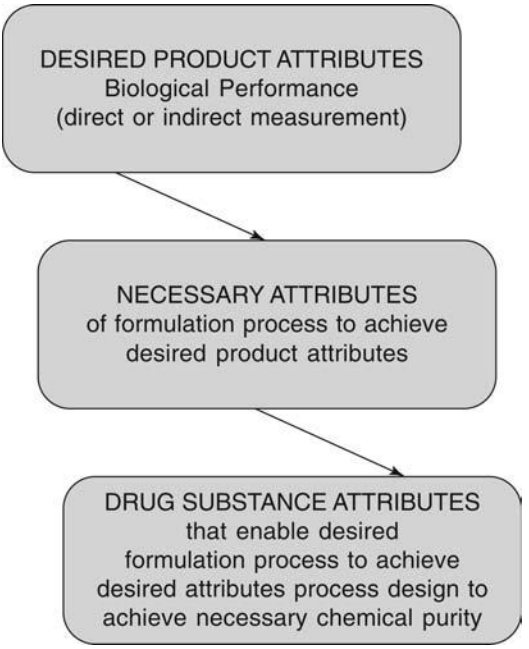

FIGURE 18.2 Design space development.

approach and examples of statistical designs. In addition, it should be noted that there are numerous computer software packages available that once familiar with the fundamentals can be employed to design and analyze experiments.

19 Process Analytical Technology

To maximize the control over any process in pharmaceutical product development, information is required on the way in which the product is responding to changes in manufacturing variables. Historically, the information was derived from data obtained on the nature of batches produced under particular manufacturing conditions. Knowledge of the batch properties were employed to modify the manufacturing conditions to ensure that the product was closely controlled to designated quality specifications.

In recent years, analytical methods and their application have improved to the point that real time in process measurements can be taken and fed back through control systems to the input parameters to allow for continuous monitoring and control of processes.

In earlier chapters, examples of the major unit operations in pharmaceutical manufacturing were outlined. These processes will now be considered with anecdotal evidence from the literature of methods that might lead to closer control of the product quality and thereby conform to recent regulatory directives to consider such methods as part of the Quality by Design (QbD) initiative.

The Food and Drug Administration has issued a guidance document on Process Analytical Technology (PAT) (Zu et al., 2007). Processes may be divided into batch and continuous approaches. These processes can be monitored by in situ, real time, and/or feedback control analyses to assure the quality of the product (Fig. 19.1).

PAT necessarily begins with the manufacture of active pharmaceutical ingredient (API) and any additives and understanding their properties (Byrn et al., 2006; Hlinak et al., 2006). Important methods in this context address the presence of impurities (including moisture), degradation products (stability), component compatibility, and crystallinity (polymorphism). Near infrared spectroscopy has been applied in situ, real time to address the chemical composition of API or additive during manufacture (Mendendorp et al., 2006). Near infrared laser Raman spectroscopy has been employed to monitor polymerization process (Francisco et al., 2006). A variety of particle sizing methods can be employed, but those that are in situ, real time employ laser scattering methods. Dosage form manufacturing can be optimized by direct methods of monitoring the variables involved in drying, mixing/blending (Portillo, et al., 2008), granulation (Papp et al., 2008), filling, compression (Askeli and Cetinkaya, 2008; Soh et al., 2007), and coating (Bose et al., 2006; Cogdill et al., 2007). For more sophisticated dosage forms, compatibility with packaging components is also required, but this is likely to have been considered during the preliminary experimental design optimization steps.

PAT arguably is at the intersection of design space (considered in chap. 18) and control strategy, these being the major elements of QbD. These topics have been described in Product Quality Lifecycle Implementation initiative of the International Society for Pharmaceutical Engineering (Drennan, 2008). Topics of interest in this initiative have been described in the Journal of Pharmaceutical Innovation.

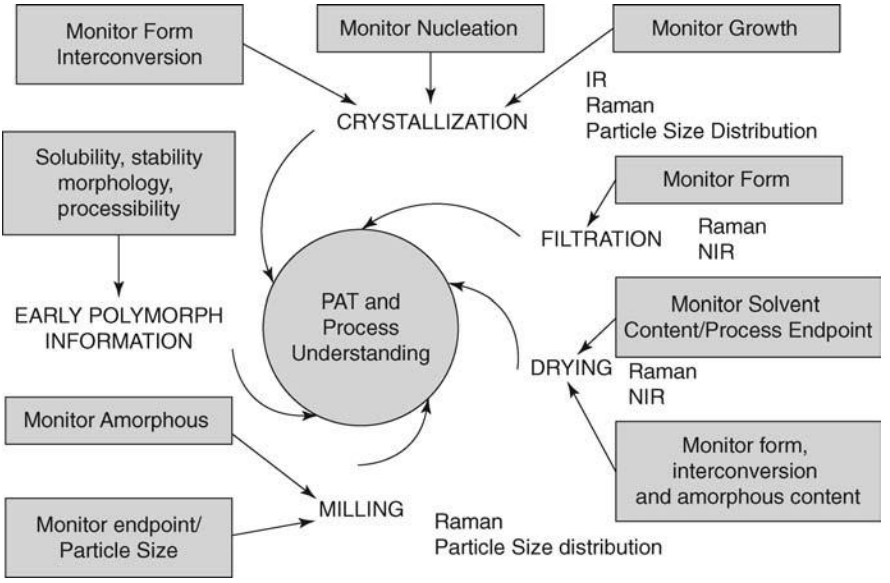

FIGURE 19.1 Critical steps in API manufacture. *Source*: Modified from Byrn et al. (2006).

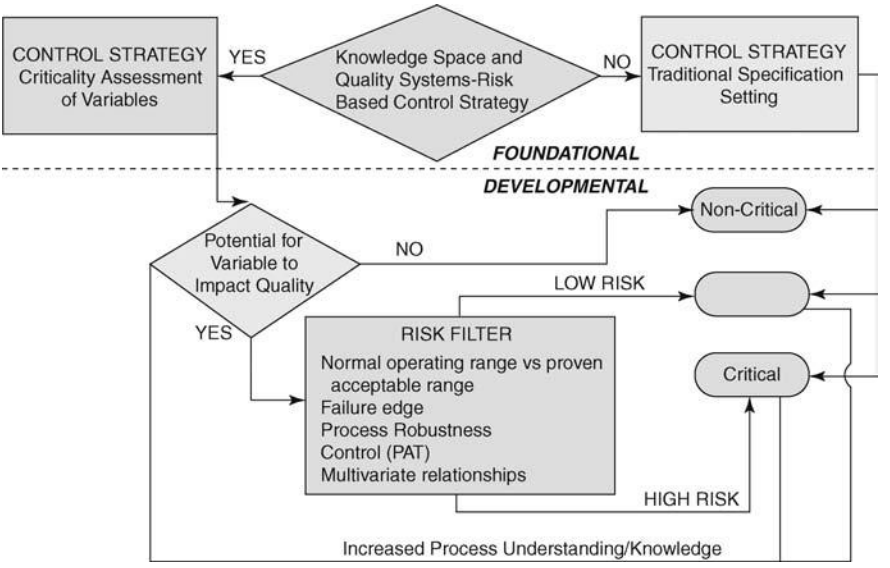

FIGURE 19.2 Decision tree to define levels of criticality. *Source*: Modified from Garcia et al. (2008).

Figure 19.2 presents the most prominent decisions required to evaluate the criticality of variables in process development. Decisions (diamonds) are made based on the business decision in foundational classification (above dotted line), and risk assessment in developmental classification (below dotted

line) that pass through a filter (rectangle) to criticality designations (rounded rectangle). With respect to criticality, those variables that are not critical have not been demonstrated to impact on safety or efficacy or factor into critical quality attributes (CQA) as defined by ICH Q(8) R and consequently do not have to be included in design space. Critical variables are those that are known to impact safety, efficacy, or other measures of biological disposition or compliance. Critical process parameters if varied beyond a certain range have a direct and significant influence on CQAs. These properties must be controlled within predesignated range to ensure final product quality. The empty symbol represents an alternative designation for attributes that may impact the product but represent a low risk. The designation of low risk is based on an indirect impact on safety and/or efficacy alone or in combination with other variables; mitigated risk; and knowledge transfer from noncritical variables requiring additional evaluation.

It has been suggested that criticality can be reduced to fundamental elements of severity, occurrence, and detection in a compounding manner (Nosal and Schultz, 2008). These terms can be related to experimental design (frequency and variation) and analytical capability (detection). During the life cycle of the product clear differentiation of levels of criticality is required to address a control strategy based on process variables, material attributes, and their relationship to quality measures.

20 Conclusion

In the previous edition of this volume a conclusion was not presented. Even for the novice to pharmaceutical process engineering the technical and practical review presented was structured in a self-explanatory manner and represented the summary of thinking over many decades in chemical and mechanical engineering. A conclusion would have added little to enlighten the reader.

This edition is intended to suggest that while many of the engineering principles described previously have not changed and, indeed, are as relevant as they have ever been, the control of the quality of the product in a demonstrable and scientifically sound fashion has become a substantial consideration in the way that processes are managed. The Quality by Design (QbD) principles espoused by regulatory bodies, unlike the fundamental engineering considerations, are evolving and are based on relatively new developments in the fields of multivariate statistics and risk management. The danger in introducing these novel concepts to an introduction to engineering principles is to dilute the clarity and well-defined nature of the former with the more general essence of the latter. However, it would be irresponsible to suggest, particularly to those coming to this topic for the first time or with limited background, that engineering principles alone are of relevance to pharmaceutical process engineering at this juncture. There can be no question that the most substantial future developments will be in new methods of analysis or data collection that can be applied through QbD strategies involving information management and statistical assessment to deliver rapid solutions to processing problems and in all probability to give real-time control of the variations in product output by manipulation of input variables.

It would be difficult to do justice to the principles of QbD, statistical experimental design, and Process Analytical Technology (PAT) without expanding the present text to a series of volumes on pharmaceutical process engineering. However, by including them as overviews, sufficient attention is given to these topics to give the novice a framework from which to continue to evolve an understanding, as their importance in product development activities increases.

In concluding this volume, a model is proposed for the relationship between the various components described and their application to process development. Figure 20.1 depicts the unit operations, shown originally in Figure 20.1 of chapter 1, and indicates the role that well-designed experiments followed by monitoring and control strategies may play in assuring the quality of the product and, thereby, ensuring both the safety and efficacy of dosage forms released for use in disease therapy.

The future of pharmaceutical process engineering will relate closely to developments in material science, analytical and information technology. It is anticipated that many new developments, particularly with respect to biotechnology, will be driven by efficiency in resource utilization, time, and expense to address the medical needs of more narrowly defined patient populations, as pharmacogenomics and the principles of individualized dosing begin to drive requirements for smaller but more controlled production than

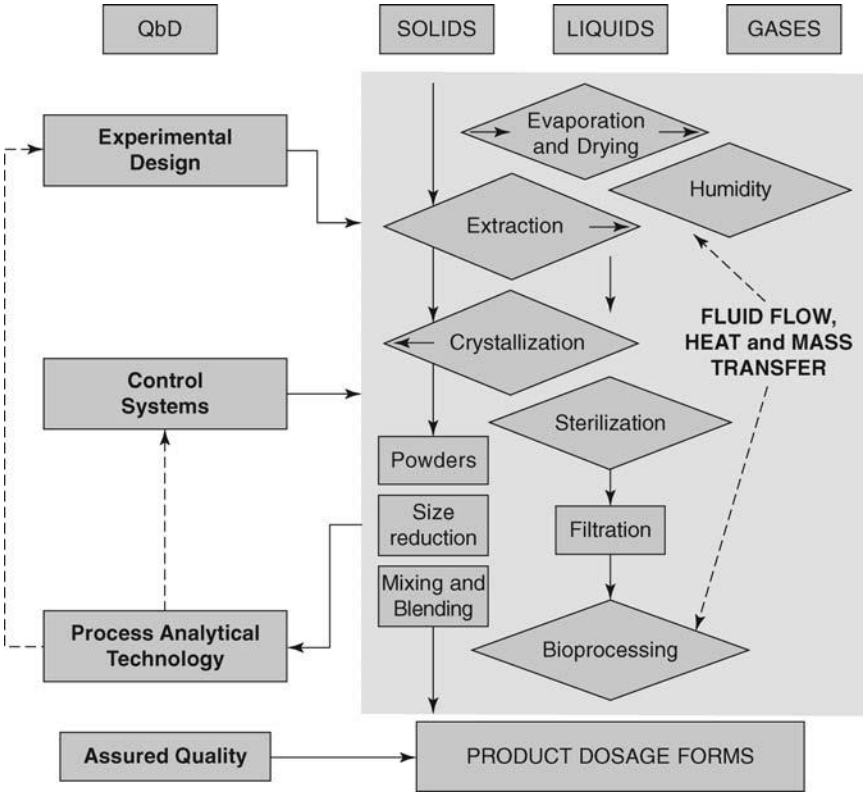

FIGURE 20.1 Monitoring and control of elements of the manufacturing process relating to product quality.

that of the 20th century. Indeed, while it may be many years before it is a common strategy, it can be anticipated that following statistically designed optimization, continuous processes under direct feedback monitoring and control could routinely be used to produce product on any required scale (for example, gram to many kilogram quantities) to supply the demand without the need for serious depletion or accumulation of stock based on the arbitrary scale of batch production. Linking production to demand based on well controlled and predictable manufacturing represents an efficient commercial strategy.