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2.1 Introduction

A model is a representation of an underlying physical–chemical phenomenon. In the pharmaceutical industry, mathematical-based models can be applied at all stages of development, starting with formulation design, continuing through process development and scale-up, and extending into process monitoring and control of the commercial process. Implementation of models offers many benefits. These include, but are not limited to, (i) enhanced process understanding, (ii) reduction of experimentation cost, and (iii) improvement of productivity and product quality.

2.2 Overview of Models

Models can be broadly categorized as either qualitative or quantitative. The focus of this chapter is quantitative models. These can be classified into three broad areas: mechanistic, empirical, and hybrid. As illustrated in the knowledge pyramid in Figure 2.1, overall understanding and the information needed to derive from these models increases from empirical to mechanistic models.

Mechanistic models are based on first principles, capture the underlying physical/chemical phenomena through sets of equations, and can be time independent (i.e., steady-state) or dynamic. As indicated by Singh *et al*. [1], mechanistic models can be an excellent way to represent process knowledge. In such models, the input–output dynamics in a unit operation can be represented by a set of differential equations. Model building necessitates the

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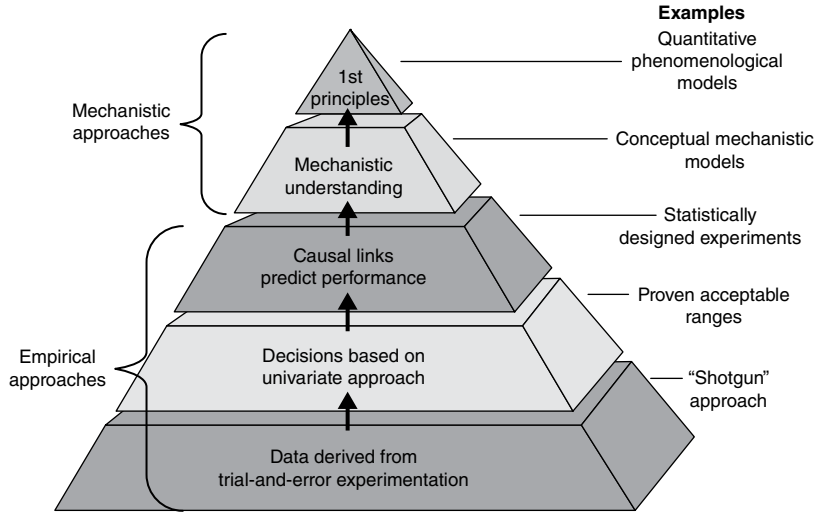


Figure 2.1 Knowledge pyramid for developing mathematical models.

availability of balance equations (e.g., mass and energy balance equations), constitutive equations, and an understanding of the constraints. Since mechanistic models are a true representation of the underlying phenomenon, predictions from these models can sometimes be extrapolated beyond the range covered by input data, depending on the validity of the underlying assumptions. Typically, the bottleneck in developing mechanistic models is coming up with equations as well as associated parameters that accurately represent the system.

Empirical modeling approaches also can be used to represent input–output dynamics. These models are particularly useful for complex systems where it is not feasible to develop mechanistic models. Empirical models treat a system as a "black box" and do not typically describe the underlying physical–chemical phenomena. These models represent input–output dynamics of a system solely in terms of observational data. One of the limitations of empirical models is that the range of applicability of these models is limited to the variation represented in the data that was used to derive the model. Hence, predictions from these models cannot be reliably extrapolated beyond the range covered by the input data. On the other hand, the advantage of empirical models is that they can be relatively easy to put together and solve, as compared with mechanistic models.

In the pharmaceutical world, empirical models are typically used for process understanding and control, such as to program software sensors associated with process analytical technology (PAT)-based tools. While mechanistic models have a distinct advantage of a wide range of predictive potential, not all

processes associated with the pharmaceutical industry are understood well enough to allow them to be modeled using first principles.

Philosophically, however, there are few true mechanistic or empirical models. All mechanistic models have a degree of empiricism in them (e.g., modeling assumptions), while all empirical models have a mechanistic element (e.g., rationale for selection of input parameters that are used to derive the models). In general, models are classified into either category depending on the preponderance of mechanistic or empirical components in the model. Following this philosophy, models can be classified as semiempirical or hybrid if they have relatively equal proportion of mechanistic and empirical elements.

Hybrid models are a combination of mechanistic and empirical models. As elucidated by Gernaey *et al.* [2], the approach is to include all available process knowledge in a first-principles-based model, where the gaps in process knowledge are then represented on the basis of empirical (i.e., data-driven) approaches utilizing available experimental data. Examples of hybrid models are scale-up correlations, where the form of the equation is derived from fundamental relations, while the constants are fit from experimental data.

As shown in Figure 2.2, each model category has several potential approaches and mathematical techniques.

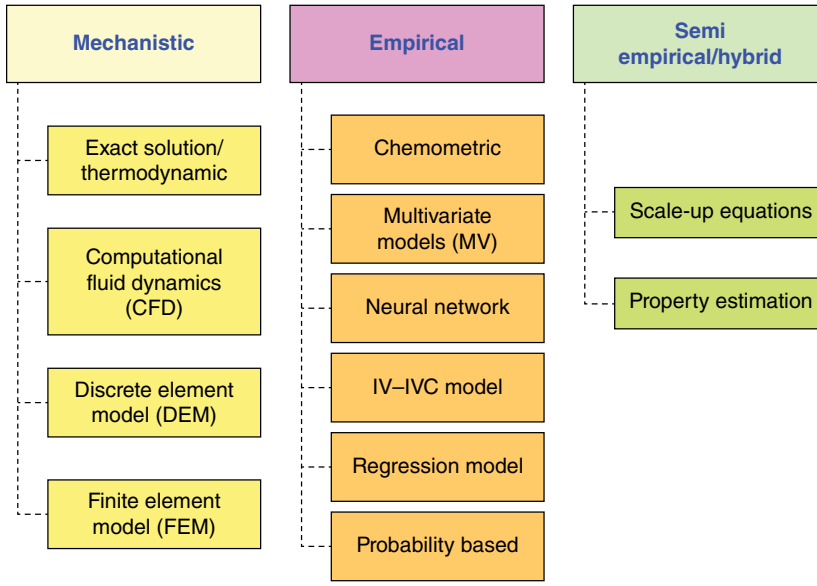


Figure 2.2 Schematic of types of models.

Mechanistic models can include, but are not limited to, (i) models that involve exact solution of equations representing the underlying physical–chemical phenomena while treating the system as one entity; (ii) computational fluid dynamics (CFD) approach, where intensive computational techniques are used to simulate fluid movements while dividing the volume occupied by the fluid into discrete cells (or the mesh); (iii) discrete element modeling (DEM) approach, which involves rigorous computation to simulate the motion of a collection of discrete particles of micrometer-scale size and above; and (iv) finite element model (FEM) that involves solving constitutive equations for a domain by discretizing the domain into small elements or nodes.

Empirical models can include, but are not limited to, (i) regression correlations (linear or nonlinear) derived between a dependent variable and one or more independent variables, (ii) statistically based latent variable (LV) models that relate a set of manifest variables to a set of LVs (multivariate models and chemometric models belong to this category), (iii) neural network models that utilize nonlinear statistical modeling tools to represent complex relations between inputs and outputs, (iv) probability-based models in which the relationship between inputs and outputs is expressed in terms of probability theory, and (v) *in vitro–in vivo* correlation (IV–IVC) models that describe the relationship between an *in vitro* property of an extended release dosage form and a relevant *in vivo* response, for example, plasma concentration. IV–IVC models include regression correlation approach as well as principles of statistical moment analysis.

Scale-up correlations based on dimensional analysis can be considered hybrid models. Dimensional analysis is based on characterization of a process in terms of dimensionless numbers. Dimensionless numbers involve a mechanistic component in identifying the factors that constitute them; however, the method of derivation of these numbers may be regarded as empirical. The objective during scale-up is to keep the dimensionless numbers constant at various scales to ensure consistency of product quality at all scales. An example of a hybrid modeling approach is the model described by Chen *et al.* [3]. This model is used for predicting active pharmaceutical ingredient content uniformity for a drug product in which the active is coated onto a core tablet. The model is based on a mechanistic description of the spray coating process in a perforated coating pan and included a number of parameters that were measured from experimental runs.

2.3 Role of Models in QbD

An example of a QbD implementation approach as outlined in ICH Q8 (R2) [4] involves the following steps:

1) Identification of quality target product profile (QTPP), which ensures the finished product's quality, safety, and efficacy

2) Identification of critical to quality attributes (CQAs)
3) Risk assessment
4) Determination of design space
5) Implementation of the control strategy
6) Continual improvement

The following paragraphs describe how models can be used at every stage of the QbD implementation approach by citing examples from published literature. This compilation is not exhaustive of various types of models that can be implemented to support QbD-based development. Instead, a few examples were selected from the literature to exemplify potential applicability for each step.

2.3.1 CQA

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired drug product quality. CQAs are generally associated with drug substance, excipients, intermediates, and drug product. CQAs of typical drug substance include particle size, residual solvent level, impurity levels, crystal form, and so on. In general, CQAs of a drug product are similar to the attributes that are part of the specifications, such as assay, content uniformity, dissolution, and impurity level.

One example using these models to better understand a CQA is the use of an IV–IVC that can be used to establish the link between desired clinical performances, that is, bioavailability and dissolution. IV–IVC has been defined as a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and its *in vivo* response [5]. In Rossi *et al.* [6], it is shown how IV–IVC data is used to develop and validate a dissolution test for immediate release ritonavir soft gel capsules (Norvir®). With ritonavir being a poorly soluble drug, dissolution is regarded as a predictor of *in vivo* performance, hence may be classified as a CQA. As shown in this chapter, a meaningful dissolution test (that includes test conditions as well as specification) for Norvir soft gelatin capsules was developed using *in vivo* data. A significant linear level A correlation between *in vitro* and *in vivo* parameters was established.

2.3.2 Risk Assessment

As outlined in ICH Q9 [7], risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product life cycle. During development, risk assessment can be carried out to identify unit operations or drug substance synthetic steps as well as material/process parameters that have an impact on the finished

product attributes. The identified parameters can then be further evaluated via either experiments or mathematical models or a combination of both.

Various quantitative or semiquantitative approaches can be used for risk assessment. ICH Q9 lists several tools that can be used for risk assessment, such as failure mode effects analysis (FMEA), failure mode effects and criticality analysis (FMECA), fault tree analysis (FTA), hazard analysis and critical control points (HACCP), hazard operability analysis (HAZOP), preliminary hazard analysis (PHA), and risk ranking and filtering.

Out of the listed tools, FMEA and FMECA can be regarded as semiquantitative approaches. These tools are commonly used for quality analysis of processes, such as those covered in six-sigma approaches. In FMEA, the risk of failure of each parameter is evaluated on the basis of frequency of occurrence (O), probability that the failure would remain undetected (D), and its severity (S). Each mode is then ranked by a group of cross-functional experts on a linear scale (e.g., a scale of 1–10), with a higher number representing a higher risk. Once the occurrence, detection, and severity are determined, the net risk is then estimated by calculating the risk priority number (RPN), which is a product of the scores for O, D, and S. A high RPN implies a greater risk.

A review of the literature showed an example where FMEA technique was implemented to improve the efficiency of a near-infrared (NIR)-based analytical procedure [8]. In this chapter, an NIR analytical procedure that was used for screening drugs for authenticity was subjected to an FMEA analysis. Each failure mode was ranked on estimated frequency of occurrence (O), probability that the failure would remain undetected later in the process (D), and severity (S), each on a scale of 1–10. Failure risks were calculated by $\text{RPNs} = \text{O} \times \text{D} \times \text{S}$. Failure modes with the highest RPN scores were subjected to corrective actions and the FMEA was repeated. Human errors turned out to be the most common cause of failure modes. Based on their findings, the authors recommended that for analytical method validation, risk analysis, for example, by FMEA, be carried out in addition to the usual analytical validation, to help in detecting previously unidentified risks. In another case, FMEA was used to identify critical formulation and process variables for a roller compaction process, and the information from FMEA was then used to build a design space by Design of Experiment (DOE) [9].

2.3.3 Design Space

As defined in ICH Q8 (R2) [4], a design space is a multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Often, risk assessment techniques are used to identify parameters that define a design space by identifying parameters that have a potential to impact the CQA of a drug quality. A design space can be determined via experiments and modeling at laboratory, pilot, and/or commercial scale. Design spaces can be

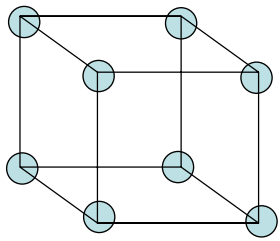
defined for both drug substances and drug products. Modeling approaches such as mechanistic, empirical, or hybrid can be used for design space development wherein as discussed in the following examples, models can be used to support its various facets, including defining a design space at pilot scale based on DOE data, scaling up pilot scale design space to commercial scale, and understanding the limitations of the proposed design space.

a) *Design space based on DOE data*: As presented by Verma *et al*. [10], the effects of key formulation process variables for a microfluidization unit operation was investigated via fractional factorial statistically based DOE. Microfluidization was used in the preparation of nanosuspensions for poorly water-soluble drugs. Multiple linear regression and ANOVA techniques were employed to analyze the data from the DOE, in order to identify and estimate the effect of important factors, to establish their relationship with CQAs, and to create a design space and a predictive model of the microfluidization unit operation. Interactions between the variables were also depicted using contour plots.

   Figure 2.3 shows a general approach for defining a design space based on DOE data. A DOE is initially carried out in terms of multiple independent input variables (i.e., inputs variables are all orthogonal to each other). Input variables are selected on the basis of the magnitude of their potential impact to product quality. Various options are available for DOE design, for example, full factorial and d-optimal. Experiments are carried out in a random fashion and response(s) is measured. Typically identified CQAs are measured as responses in a DOE. Data from the DOE is analyzed using statistical approaches such as Pareto charts to identify the statistical significance of input variables and their interactions to product quality. A regression correlation is then derived from the DOE data in terms of the significant input variables. Design space can then be represented mathematically in terms of the regression correlation or graphically, for example, as a contour surface.

b) *Design space based on hybrid model*: In this example, two mechanistic tablet film coating models were used for scale-up of tablet film coating of an established commercial immediate release product [11]. The models were the following: (a) a thermodynamic film coating model based on the first laws of thermodynamics and mass and energy balance principles that predicted exhaust air temperature and relative humidity on the basis of input conditions and (b) a physics-based film coating atomization model that described the performance of atomizers utilized in the tablet coating process. The models were used to establish an acceptable range of process parameters in a new film coater to match the proven acceptable range of operating conditions in the existing pan coaters. These are considered as hybrid models, since each model included some empirical parameters that were fitted using experimental data, to minimize the residual sum of

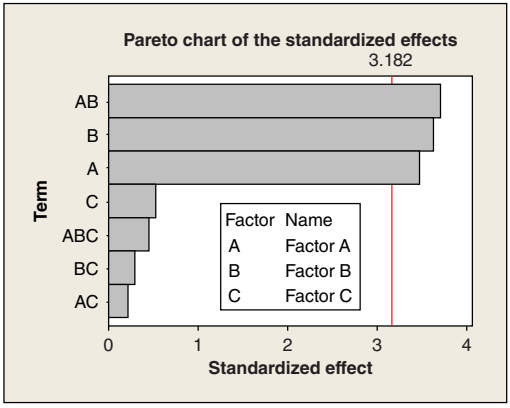
(a)



(b)

Experiment	Factor A	Factor B	Factor C
1	+	–	–
2	–	+	–
3	+	+	+
4	+	–	+

(c)



(d)

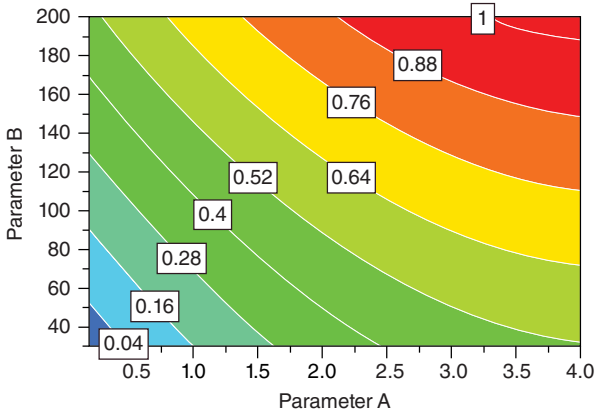


Figure 2.3 Approach for developing a design space based on DOE data. (a) Choose experimental design (e.g., full factorial, d-optimal), (b) conduct randomized experiments, (c) analyze data (determine significant factors), and (d) define design space (e.g., contour surface).

squared error between experimental data and model prediction. The established process parameters were then used to prioritize the experimental design to minimize the number of required trial runs and to support optimization. The recommendations were then provided to the commercial site to guide the design of scale-up trials.

c) *Design space based on integrated multivariate approach*: In another case, a design space was defined on the basis of DOE, optimization, and multivariate analysis (MVA) [12]. Initially, a screening DOE was carried out to identify the parameters that have an impact on the finished product's CQA. Following the screening DOE, an optimization DOE was carried out to evaluate the effects of the design factors on manufacturability and final product's CQA such as tablet blend flow and tablet dissolution and to establish a design space to ensure CQAs. Figure 2.4 is a schematic rendition of the methodology for design space development and implementation, as presented by Huang *et al.* [12].

   As illustrated in Figure 2.4, design space was established as a response surface model based on DOE data. In addition, an MVA using principal component analysis (PCA) and partial least squares (PLS) was also carried out using all the variables from the DOE campaigns, to study multivariate relationships between *all* variables that include raw materials, intermediates, various unit operations, and final product. The multivariate techniques were complementary to DOE analysis and provided a representation of all multivariate interactions in the process, based on the combinations of all raw materials and process parameters. Findings from both DOE and MVA were then used to define a control strategy for the product. As elucidated by Huang *et al.*, the combined use of DOE and MVA offers a robust mechanism to explain complex multivariate relationships. Since DOEs in general deal with a limited number of experiments (due to practical limitation in the number of experiments), MVA can be considered as complementary to DOE, providing additional information about the product and processes.

d) *Mechanistic model for scale-up*: In an example by Pandey *et al.* [13], a DEM was developed to study the particle motion in pan coating. DEM simulates the prediction of individual trajectories of particles using constitutive equations. By this approach, movement due to the contact forces from neighboring particles is accounted for. An advantage of this approach is that it allows to study the changes in particle motion due to changes in operating conditions (e.g., pan speed and pan load) as well as particle properties such as tablet size, shape, and density. On the basis of DEM analysis, a modified scale-up relationship for the pan coater was proposed.

e) *Monte Carlo-based models for understanding uncertainty in design space*: A Monte Carlo-based method was applied to simulate the propagation of uncertainty in predictions performed with DOE-based design space models

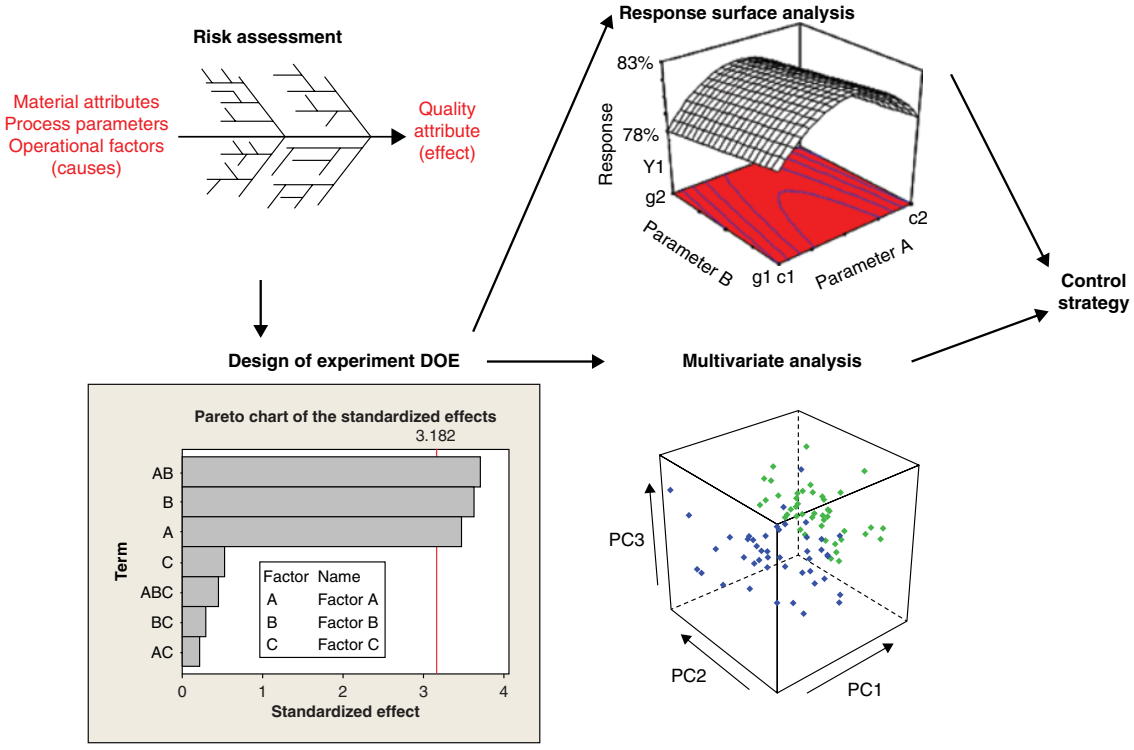


Figure 2.4 Approach for defining a design space based on DOE and MVA.

by Kauffman *et al*. [14]. In this study, the design space was represented by a polynomial model. The results of the simulations presented in this work highlighted two major benefits from the application of Monte Carlo simulation for the propagation of uncertainty in design space models. First, the simulations provided estimates of both the means and standard deviations for the predicted values of CQA. With these quantities in hand, design space was then specified on the basis of model predictions and product quality specifications with statistically meaningful confidence levels. Secondly, the simulations identified the process variable variances that have the greatest influence on the product quality variance, which can be used to prioritize control strategy and process improvement plans.

2.3.4 Control Strategy

In ICH Q10 [15], a control strategy is defined as a set of controls, derived from current product and process understanding, that assure process performance and product quality. ICH Q10 is a model for the pharmaceutical quality system that can be implemented throughout the life cycle of the product. The objective of the control strategy is to ensure that desired quality product will be manufactured. In general, a control strategy includes the following components: specifications for incoming materials and critical intermediates, ranges for process parameters, in-process monitoring and control, end-product testing at release, and other elements as described in Q10 such as change management. Furthermore, a control strategy can evolve/change during the life cycle of a product. Management of these changes is typically handled by the firm's change management procedures.

Models can be used in the implementation of a robust and efficient control strategy. In general, such models have to be updated throughout the life cycle of the product, and procedures for maintenance of these models are typically captured in the firm's change management system. Some examples of these models to support control strategy are presented as follows:

a) *LV-based models for process control*: In the example by Kourti [16], an LV approach is used to support a feed-forward control strategy. Using this approach, when a deviation is detected in the measured quality of an intermediate that could affect finished product quality, a feed-forward control strategy could be used to adjust manufacturing parameters to produce the desired quality of the finished product. An example of this approach is adjustment of tablet compression parameters based on granule bulk density. An LV model is built from multiple batch data to relate the finished product quality in terms of compression parameter settings and intermediate material attributes, for example, granule density. This LV model, as illustrated in Figure 2.5, shows the interaction between compression process parameters and intermediate material attributes [17].

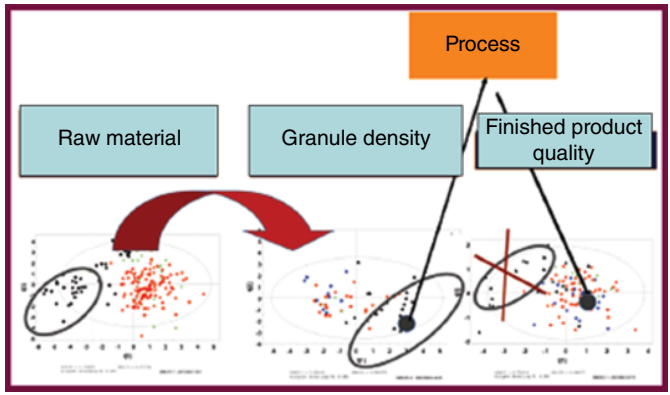


Figure 2.5 Approach for developing LV models for feed-forward control. *Source*: Kourti [17]. Reproduced with permission of John Wiley & Sons.

In another example by García-Munoz *et al.* [18], LV models were used to set quality-driven specifications for incoming raw materials. Such specifications accounted for the inherent variability in the process and the combined effect of materials with process conditions onto product quality. Additionally, Rathore *et al.* [19] demonstrated the usefulness of multivariate data analysis techniques for optimizing biopharmaceutical manufacturing, process scale-up, process comparability, and process optimization.

b) *Multivariate statistical process control* (*MSPC*) *model to support real-time release testing (RTRT)*: In ICH Q8 (R2), RTRT is defined as the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. Skibsted *et al.* [20] have demonstrated how two MSPC-based models derived from data measured by two NIR instruments were used to provide an early warning during granulation and to separate good batches from potentially bad batches.

2.4 General Scientific Considerations for Model Development

Model building typically includes the following steps [21]. These steps are usually executed in a sequential manner, but many times it may be necessary to return to an earlier step, thus imparting an iterative nature of this process. The overall steps are as follows:

- Defining the purpose/objective of the model.
- Deciding on the type of modeling approach (e.g., mechanistic, empirical, or hybrid) and the experimental methodology that would be used to support

the model development. Since any model is based on a number of assumptions, it is important to understand at this stage the limitations of these assumptions in order to correctly design the experiments and to interpret the model results.
- Collecting experimental data to support model development.
- Developing model relationships, based on the scientific understanding of the process and the collected experimental data.
- Assessing the validity of the model prior to implementation, by both internal metrics and external validation.
  - Internal validation involves comparing model prediction with the actual values, using the same data set that was used to build the model. Various techniques such as cross-validation, random (Monte Carlo) resampling, and boot strapping can be used for internal validation [20].
  - External validation involves verification of model results with independent data set(s), that is, data that was not used to build the model. Verification of the model with an appropriate data set is especially important for empirical models to demonstrate the robustness of such models. Model validity is typically measured in terms of goodness of fit.
- Documenting model results including initial assumptions and developing plans for maintaining and updating the model throughout the life cycle of the product.

Additionally, some specific considerations are warranted when considering the implementation of models for specific purposes, as discussed in the following text.

2.4.1 Models for Process Characterization

Process characterization models can include models for process optimization (e.g., reaction kinetics model), design space determination, and scale-up. Since the term design space in general refers to a multidimensional hyperspace, it is important that models defining a design space consider multivariate interactions. In addition, for both mechanistic and empirical models, significant uncertainty can exist in the model predictions, due to the underlying assumptions and simplifications used in model derivation, variabilities in measurements in the supportive data, and error in the model fit. Evaluation of uncertainty in a design space model can lead to a more robust design space and can help identify appropriate risk mitigation steps when moving to areas of uncertainty.

Typically, if a model to define design space is developed based on laboratory or pilot scale data, it is then verified at commercial scale. Verification approaches in general consider the scale dependencies of the model parameters, the modeling approach (i.e., mechanistic or empirical), and the control strategy.

2.4.2 Models for Supporting Analytical Procedures

This category includes models used to support various PAT-based methods. In general, these are data-driven chemometric models such as PCA or PLS. These models often have the flexibility to handle noisy measurements, missing data sets, and highly correlated variables. A primary consideration when developing such models is the quality of data used to derive and to validate the model. To make a robust chemometric model, the data set should include an appropriate range of variability. For example, chemometric models meant to span a design space should contain data representative of variations within the design space.

2.4.3 Models for Process Monitoring and Control

When developing models for process monitoring and control, it is important to consider all pertinent quality attributes and in-process measurements using techniques such as risk assessment. For example, if prediction from an empirical model (e.g., LV model) is used to ensure that the process is manufacturing desired quality product when operating within the design space, it is desired to include all expected sources of variability during the model-defining stage. Including variations helps ensure that the model would be applicable to all regions within the entire design space for occurrences of material and process parameter variability. Alternatively, if the objective is to control the process in a narrow range near the target operating condition using an LV model, the model could be constructed using batches manufactured only near the target condition.

2.5 Scientific Considerations for Maintenance of Models

Typically, models may need to be updated due to an instrument or process drift. Additionally, unaccounted for variability (e.g., changes in raw material) could result in out-of-spec predictions from the model. Consequently, it can be valuable to monitor the performance of the model over the life cycle of the product. An approach for monitoring model performance could include periodic comparison of model prediction with a reference method. This approach would allow making adjustments to the model (e.g., recalibration) before failures occur.

The approach of model maintenance and update is relative to the model implementation strategy (i.e., importance of the model in the control strategy and its potential to affect product quality). Clear metrics for model update can be established depending on the level of risk of the model.

2.6 Conclusion

In the QbD paradigm, mathematical models can be an important tool for leveraging pharmaceutical process understanding and can be applicable throughout development and manufacturing including process development, scale-up, process monitoring, and continual improvement. Use of models can support efficient development and implementation of a robust process that ensures consistent manufacture of desired quality product. Although many such models have been implemented in pharmaceutical process development and manufacture, by and large these modeling approaches are still evolving and more understanding is expected to be garnered in the coming years.

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