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Scientific and Regulatory Considerations for Implementing Mathematical Models in the Quality by Design (QbD) Framework

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This article presents points to consider for building and using models in the regulated pharmaceutical industry and offers examples of how models can play a part in the Quality by Design (QbD) framework.

A model, in general, is an alternative representation of reality. A mathematical model is a description of a system using mathematical language. Mathematical models are used extensively in process industries to describe the chemical and physical phenomena taking place during production. There are models to describe chemical reactions, crystallization, distillation, and a plethora of other operations; models that predict quality properties based on process data, i.e., soft sensors, as well as models that are used in Process Analytical Technology (PAT) applications.

The Quality by Design (QbD) framework for drug development and manufacturing is a science and risk-based approach that begins with predefined objectives for meeting the desired clinical performance and emphasizes product and process understanding and process control.[1] In the QbD framework, mathematical models can be used at every stage of product development and manufacturing. Models have been implemented in pharmaceutical industry for developing and controlling processes and have appeared in regulatory submissions.[2] Models also can be indispensable for the implementation of continuous manufacturing processes. Overall, application of models throughout a product's life cycle from development through manufacturing can enhance process and product understanding. In general, these modeling approaches are still evolving in the pharmaceutical industry.

There are many considerations in the development, validation and maintenance of models depending on their use. This article provides points to consider for the building and use of models in the regulated pharmaceutical industry. It offers examples of how models can play a part in the QbD framework, how these models can be developed, and how model information can be utilized as a part of the control strategy.

Overview of Models

Mathematical models may be first principles or mechanistic models, empirical, or hybrid. First principles models can be derived when the underlying physical, chemical or biological phenomena are thoroughly understood and expressed in the form of equations; the Arrhenius equation and the Lambert-Beer Law are examples of first principles relationships. In addition to ample history on first principles models that appear in the science and engineering literature, there have been several publications in the literature that describe potential applications to the pharmaceutical industry,[3]

including, modelling for chemical reactors, crystallization, distillation, drying, and a plethora of other unit operations in the pharmaceutical realm.

Empirical models are data based models. Depending on the objectives, different types of empirical models can be derived; the type of data required to derive such models also depend on the objectives of the model. Causal empirical models are derived from data collected from Design of Experiments (DOE); for example, models used to derive design space from Design of Experiments (DOE) as well as PAT based calibration models (i.e., spectral NIR) are causal models. Other types of empirical models are those models that are derived from historical data collected on a process that may be used either for troubleshooting or for Statistical Process Control (SPC), including Multivariate Statistical Process Control (MSPC). When used for troubleshooting, all data collected over a historical period are projected on to the latent variable space to give an initial idea of clusters, outliers, unusual process periods, and other patterns to aid postulating reasons for differences. When models are used for SPC and for continued process verification, the typical operating region and control limits are well defined; historical data on good production and the typical operating region can be used for setting the limits to detect common cause variation for SPC type modelling.[19]

Hybrid models, as is evident from their name, combine theoretical knowledge with empirical data. One example of a hybrid model is presented for the design of a control strategy for control of Particle Size Distribution (PSD) in a semi-batch emulsion polymerization process.[4] A hybrid modelling approach was used for batch-to-batch optimization in which a fundamental population balance model describing PSD evolution is augmented by a Partial Least Squares (PLS) model.

The choice of the model (first principles, empirical, hybrid) depends not only on the modelling objective and the theoretical background available, but also on other criteria. For example, while there exists knowledge for detailed models for crystallization based on population balances, a DOE model based on empirical data may be chosen to be fit for purpose, based on the objective and business criteria. Finally, theoretical models can be used as directional models to aid DOE.

Models can be implemented at any stage of the product lifecycle. For the purposes of implementation, models can be classified on the basis of intended use of the model. Examples of different categories based on intended use are:

a. *Models for supporting process design:* this category of models includes, but is not limited to, models for: formulation optimization, process optimization, design space determination and scale-up.
b. *Models for supporting analytical procedures:* this category includes empirical models based on data generated by various Process Analytical Technology (PAT) based methods; for example, a calibration model associated with a NIR based method.
c. *Models for process monitoring and control:* this category includes, but is not limited to:
   - Univariate or multivariate statistical process control (SPC or MSPC) models: these models are used to detect unusual variability that is causal; the model is usually derived and the limits are determined using batches manufactured only at the target condition and producing acceptable product.
   - Models used for process control (e.g., feed forward or feedback). An example is feed forward model to adjust compression settings on the basis of incoming granule material properties. An example of feedback model routinely encountered in the pharmaceutical industry is adjusting compression force on the basis of measured tablet weight.

Within each implementation mode, for the purpose of regulatory consideration, an important factor to consider is the model's contribution in assuring the quality of the product. In that context, models can be classified as high, medium or low impact:[5]

a. *High Impact Models:* a model can be considered high impact if prediction from the model is a significant determinant of quality of the product (e.g., a chemometric model for product assay, a surrogate model for dissolution).
b. *Medium Impact Models:* such models can be useful in assuring quality of the product, but are not the sole determinant of product quality (e.g., most design space models, many in-process controls).
c. *Low Impact Models:* these models are typically used to support process and product development and design efforts (e.g., formulation).

Use of Models in a QbD Framework

The steps in the product lifecycle in a QbD Framework are given in Figure 1. Modelling is an integral part of QbD and there can be models that are involved in every step. Ex-

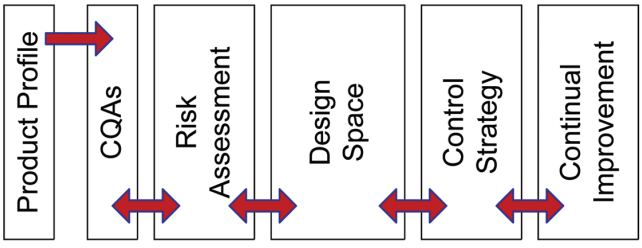

Figure 1. Modeling can be an integrated part of all stages in a QbD framework.

amples of the types of models relevant to each step of the product's lifecycle are discussed below:

Establishing Critical Quality Attributes

Once the quality target product profile is established, the next step is to define the product Critical Quality Attributes (CQAs).

In Vivo vs. *In Vitro* Correlation (IVIVC) models establish *in vitro* dissolution criteria by relating the CQA of dissolution to *in vivo* performance. IVIVC models are derived by evaluating relationships of exposure data to formulation attributes, such as disintegration or dissolution. These attributes can serve as surrogates for the various biological processes that comprise the total pharmacokinetics of a given drug product. Such modelling attempts have already been discussed in the literature.[6] A number of alternatives, such as Physiologically Based Pharmacokinetic (PBPK) models, also have been proposed.[7]

Risk Assessment and Risk Mitigation

Modeling can be a very useful tool to provide knowledge and support risk assessment and risk mitigation. Various types of models can be used for this purpose, from qualitative models that show directions of effects for a preliminary assessment to more complicated models that can be used in control strategy, as discussed later. Commercially available Computational Fluid Dynamics (CFD) software packages can be used to simulate a variety of applications, including spray drying, inhalation, mixing in agitated vessels and flow of granular material; such models may provide preliminary directional information, set strategies for DOE and then, combined with DOE, provide quantitative information that aids process understanding. As an example, CFD models may be used to understand the mixing properties of a non-traditional vessel layout and decide locations of placing sensors, such that sampling is representative of the process conditions. CFD can be used in assessing mixing sensitive chemistry to establish the role of vessel specific configurations in reaction selectivity. Other models like mass and energy balances can be used to guide DOEs.

The use of modelling to provide knowledge for mitigating risk was demonstrated in the following example.[8] The risk assessment provided a picture of the risks related to solid state form control and drying; a thermodynamic model, provided by commercially available software, was used to describe the behavior of a system, and to demonstrate that it was not thermodynamically possible to achieve an acceptable total residual water result and an unacceptable isopropanol result. Note that this model assumes no bound or trapped water in the solids. Hence, it was shown that it was possible to assure that residual isopropanol levels will meet acceptance criteria, solely by assay of the residual water content by Karl Fisher. (The risk of unacceptable isopropanol was avoided simply by controlling residual water.) The model was tested at scale using on-line dryer dew point measurements. It was concluded from the phase diagram that the thermodynamic model showed low risk of failure if the drying time was more than three hours for that specific equipment and by using a temperature of 45°C under vacuum conditions without specific control of humidity.

Design Space

A design space can be expressed as a function that relates quality to the raw material attributes and the process parameters:

$$Quality = f(raw\ material, process\ parameters)$$

or more specifically as:

$$[q_1,q_2, \ldots q_N] = f(z_1,z_2, \ldots z_K, x_1 1, x_1 2, \ldots x_1 M, \ldots x_N 1, x_N 2, \ldots x_N P) + Noise \quad (1)$$

When the design space is expressed in the form of equation (1) and the raw material attributes are varied, it is possible to solve for the combination of process parameters ($x_1 1, x_1 2, \ldots x_N P$) that will result in the desired set of quality attributes q_1, q_2, q_N given the values of the raw input material characteristics z_1, z_2, z_N.[9] Notice that equation (1) can be written for one quality attribute q_N or for multiple quality attributes simultaneously.

The concept of the design space is illustrated with the following simple example. In Figures 2 and 3, we have a process where the raw material is described by two attributes z_1 and z_2 (for example, for drug substance these could

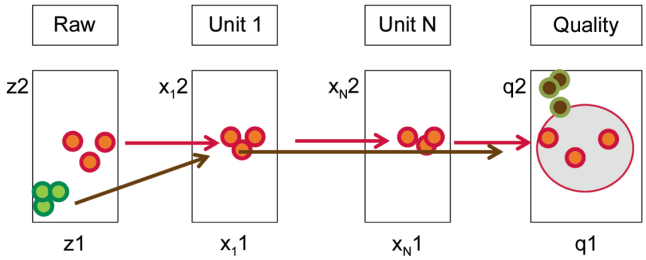

Figure 2. By maintaining fixed process conditions, it is possible to propagate raw material variability to quality.[9] (Reprinted with permission of John Wiley & Sons, Inc.)

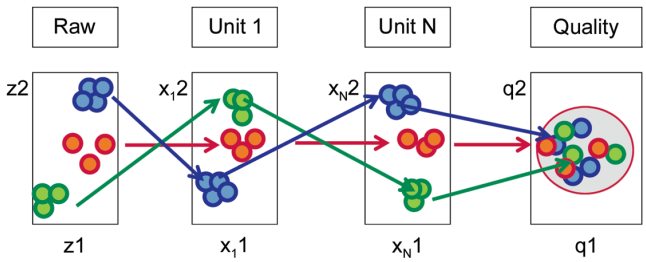

Figure 3. By taking a feed forward approach where the process conditions are flexible to account for raw material variability, we can maintain quality on target.[9] (Reprinted with permission of John Wiley & Sons, Inc.)

be particle size and density), quality is described by q_1 and q_2 (for example, dissolution and content uniformity), and unit operations described by process parameters x_{11} and x_{12} for unit 1 (for example, unit 1 could be high shear wet granulation, process parameters could be total water and addition time, or water and total work) and process parameters x_{N1} and x_{N2} for unit N (for example, main cylinder height and press speed for compression). The big circle in the "Quality" box represents acceptable quality. Two material attributes, two quality attributes, and two process parameters per unit operation are used for illustration purposes, but this does not affect the generalization of the following discussion to more variables. Each small circle represents the values of these parameters or attributes for one batch. Figure 2 shows what happens when a fixed process is considered, depicted by the red circles. Suppose that we have raw material for three batches at a selected range of (red circles) properties and we run the traditional three batches at selected range of process parameters (red circles for units 1-N) and we achieve the target quality (all red circles representing quality fall on a multivariate target). The green circles in z_1 - z_2 represent raw material from a different manufacturer and with attribute values different than the range initially examined. If we process the green material on the fixed process conditions (e.g., in the process range of the red circle values in units 1-N), there is a potential that the final quality (green circles in quality) will differ from that produced by the red raw material. Figure 3 illustrates that if we judiciously choose to operate at appropriate different process conditions for each different material (green path for the green raw material attributes and blue path for the blue raw material attributes), we can have quality on target. In other words, there is a multi-dimensional combination of raw material and process parameters that assures quality.

The model used to describe the design space may be based on first principles/mechanistic approach or may be empirical as derived from design of experiments or may be a hybrid. The choice of the type of model depends on the objective and the theoretical background available to describe the principles of the unit operations. Empirical models used to describe a design space should be causal and therefore derived from carefully designed experiments. Some DOEs also may be necessary in order to estimate parameters if mechanistic models are used. Together with the model, one has to specify the range of parameters over which the model would be expected to be valid. Therefore, in this case, the design space is the model (relationships seen by paths in Figure 3) plus the range of parameters for which the model have been verified.

A design space described with the above concept (equation (1) and paths of Figure 3) can be derived to cover a wide range of raw material characteristics and process conditions. Such an approach gives flexibility in raw materials choices, as it allows for wider choices than fixed process conditions (as seen in Figure 2). It demonstrates that for a defined set of quality values (q_i), a wide range of raw material attributes can be accommodated, provided that for each combination of material attributes, specific process conditions are used (within the range that the model was tested) that satisfy the equation. It should be understood that in the presence of interaction terms or if the parameters are not orthogonal to each other, random combinations of raw material attributes and process parameters (i.e., combinations that do not satisfy equation 1) may not work.

The design space model may cover one unit operation or a series of successive unit operations. Taking the tablet manufacturing process in Figure 4 for example, one may wish to derive a model to express the granule characteristics as a function of the raw materials entering granulation and the process parameters (i.e., design space for granulation); another model may be derived to express final quality as a function of the granule characteristics and the compression and coating process conditions. Finally, another model can be derived to express quality as a function of information from all unit operations and from raw material (design space for all unit operations).

Design Space for Multiple Unit Operations and/or Multiple Quality Attributes

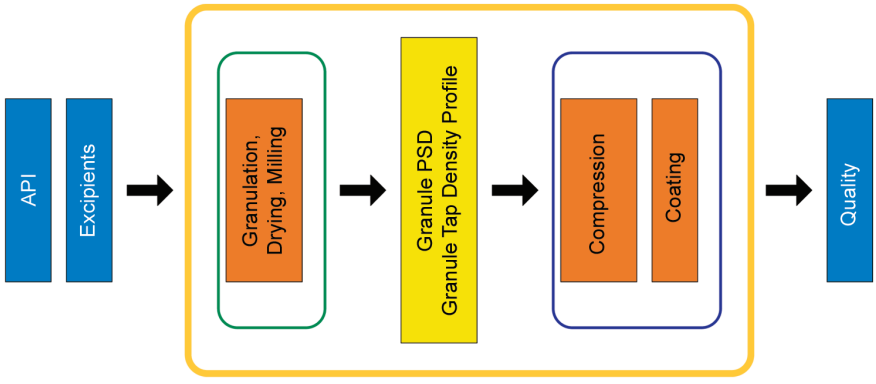

Figure 4. Different models can be derived for tablet manufacturing. The green frame represents model for design space of granulation which can be derived to express granule characteristics (granule PSD and granule tap density profile) as a function of the raw material (API and excipients) attributes and the granulation process parameters. Another model, represented by the blue frame, can be derived to express final quality as function of the granule characteristics (granule PSD and granule tap density profile) and the compression and coating process conditions. Finally, another model represented by the yellow frame, can be derived by expressing quality as a function of raw material (API and excipients) and process conditions from all unit operations. This yellow box represents design space for all unit operations.

An integrated design space, established over several unit operations, provides flexibility into the choice of control actions because the type and location of the control action can be decided based on knowledge of interactions of parameters between unit operations. Problems at later unit operations can be anticipated and corrected in earlier stages. Use of an integrated design space can provide the manufacturer with the most efficient operation, that is, higher yield or lower operating costs. In other words, the control strategy and the design space are inter-dependent, such that the control strategy can be implemented in the most cost effective way.

Recognizing the continuum in drug production that spans from the drug substance to the drug product could help create a more versatile and robust design space. All the steps and materials involved in the production of the drug substance and drug product have the potential to impact the quality of the drug that will be delivered to the patient, as they were selected with the objective to achieve a desired Quality Target Product Profile (QTPP). Therefore, the final product that delivers the active pharmaceutical ingredient to a patient is indeed the result of a multidimensional combination of raw material attributes and process parameters that span several unit operations, including the drug substance production, drug product production and packaging. Each one of the unit operations may have an impact on one or more final quality characteristics or the product stability.[9] Of course, an empirical model for design space does not express each CQA as a function of every single process parameter and material attribute, because the choice of operating procedures, ranges and controls mitigate most of the risks.

As mentioned earlier, the model described in equation (1) may express the design space as multivariate model solved simultaneously for all CQAs. This approach is commonly used in other industries where a set of unit operations are described by first principles or empirical models and optimizations are solved to determine operating conditions such that the quality is assured while considering other constraints (e.g., economic, environmental) simultaneously. Multivariate expression of finished product specifications can be defined in this manner. The overall product quality expressed as the combination of all CQAs will be a function of all the material attributes and process parameters whose variability has an effect on any of the CQAs.

For empirical design space models, it is important to keep the underlying assumptions and approaches in mind. First, the potential effect of variation of those parameters that need to be controlled but were kept constant or in a narrow range during execution of the DOEs should be considered in the plans for continued process verification of the design space model. Multivariate Statistical Process Control (MSPC) could be used to check that the ranges of these parameters are the same as those during the DOE. Additionally, if separate design space models are defined for different CQAs, the acceptable parameters and/or ranges could differ. In such cases, it is important to select design space ranges where the specifications for all the CQAs would be met simultaneously. A more comprehensive study where this was achieved by modelling all the CQAs simultaneously using advanced latent variable methods and setting multivariate specifications for the raw materials has been presented.[10]

A design space model may be linear or non-linear. In order to be able to predict intermediate quality (i.e., granule properties) as well as CQAs and also have a flexible control strategy, more than one model is typically needed for a multi-unit plant. That is, the design space for the whole process can be considered a collection of models that: 1) relate the final quality to all previous units, raw material and intermediate quality 2) relate intermediate quality to previous unit operations and raw material and 3) predict the process conditions of the next unit operation based on the preceding intermediate quality, if feed-forward control is designed in.

In Process Controls (IPCs) and Design Space

Design space is an element of the overall control strategy. An IPC that is an output from one unit operation can be an input to another. When a disturbance in unit N affects the value of the output IPC of unit N, it is wise to use the value of IPC as input in unit N+1 for feed forward process control. The value of the IPC will reflect the problem created by the disturbance. For example, say in a process we have granule particle size or granule density as an IPC; we accept their values within a specific range. Knowledge when the value is close to the upper limit or lower limit of the range will give better predictability of dissolution, even if the granule density is an IPC. An example of dissolution expressed as a function of hardness or thickness (IPCs) can be found in ISPE PQLI® example.[8]

However, the design space cannot be fully expressed with IPCs (attributes) only; the path that the process followed such that a certain attribute is achieved can be important.[11] This path is often called the "process signature."

Control Strategy

Various approaches to process control can be used as part of the control strategy and modelling plays a significant role in each.

It should be noted that the term "control" currently appears in the pharmaceutical literature to describe a variety of concepts such as: conformance to end product specifications, end point determination, feedback control, statistical process control, or simply process monitoring. For the purpose of this article, "process control" refers to a system of **measurements** and **actions** within a process intended to ensure desired quality output of the process.

In this section, two major approaches to process control are discussed:

- Feedback control, where corrective action is taken on the process based on measured deviations from the process output
- Feed forward control, where process conditions are adjusted based on measured deviations of the input to the process

Under the control strategy umbrella, there are a multitude of approaches that a company can take and for each approach there is a large number of modelling approaches possible to address different specific needs. Some example modelling activities are discussed below.

Models to Support Process Analytical Technology (PAT)

PAT can play a significant part in the control strategy by providing real time information. This information can be used for feedback or feed forward control. Empirical models are used for the data evaluation and modelling of various PAT based methods, as for example, a calibration model for a Near Infrared (NIR) based method. Commonly, chemometric models such as Principal Component Analysis (PCA) or Partial Least Squares (PLS) are used. In some cases, NIR models serve as surrogates for a primary reference method; for example, a HPLC assessment of content uniformity can be replaced by a representative NIR method. Notice that NIR based methods may use different types of models depending on the objective of the PAT application. For example, NIR can be used for water content determination utilizing PLS calibration models during a drying operation. NIR can be used for end point determination of blending utilizing rate change models;[12] but also NIR can be used for end point determination of blending by predicting the API content of the blend. Approaches for the development and validation of the model would depend on the impact of the model.

Information obtained from real time analyzers may be included in the design space, where we may have a combination of such real time values with the mechanistic or empirical model of the unit operation. For example, a model that predicts the effect of water content of granules on impurity level at release and on the shelf-life can serve to calculate constraints for the granulation design space, but also alert of a potential problem in the shelf life if atypical water content values are measured by PAT.

Soft Sensors Models

Soft sensor models are predictive models where the value of a quality variable is not directly measured, but is inferred from process data. For example, dissolution can be expressed as a function of other process parameters and material properties; such a model acts as a soft sensor for dissolution. An example can be found in the ISPE PQLI® Guide: Part 2 – Illustrative Example,[8] where dissolution is expressed as a function of drug substance particle size, magnesium stearate surface area, lubrication time and crushing force. These models are frequently data based and derived from multi-factorial DOEs.

Real Time Release Testing

Real Time Release Testing (RTRT) refers to 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.[1] In other words, RTRT refers to using the combination of material attributes and process controls as surrogates for an off-line method for end product testing. The surrogate may be an on-line (real time) analyzer, as for example NIR for residual solvents, NIR for content uniformity, or it may be a soft sensor where the quality is predicted from a number of other measurements. Empirical models are commonly used to calibrate real time analyzers or to derive models for soft sensors. Such calibration models should fulfil the requirements of any analytical QC method.

When the value predicted from a soft sensor model is to be used for release of the product, on-going process verification and maintenance of the predictive model could benefit from Multivariate Statistical Process Control (MSPC) models. Such models are used to assure that the batches on which the model is applied were produced within the typical operating range for which the model was developed, to examine that the process behavior is similar to the time when the model was developed, and to assure that the assumptions prevailing when the model was developed are still valid. Variables to include in the MSPC models are generally identified from a risk assessment study.

End Point Determination

Modelling, in combination with real time analyzers or process data, can be used for "end point detection" or "end point control." For example, models to determine % moisture from NIR are empirical models based on multivariate analysis and are used to stop drying when a certain % moisture is achieved.

Another type of an end point determination model is the Caterpillar algorithm, which works by assessing changes in the spectral data variation along time. It has been applied for real time end point detection for powder blends.[12]

Finally, through utilizing multivariate analysis and process data, empirical modelling can be used to monitor process signatures for end point determination problems.[11] This approach is a form of a soft sensor monitoring index of wellness of the process.

Feed Forward Control

The concept of adjusting the process conditions of a unit based on incoming measured disturbances through feed forward control is well known to the process systems engineering community and has been used for several decades. The methodology is also used in multistep/multi-unit processes

where the process conditions of a unit are adjusted based on information of the intermediate quality achieved by the previous unit or based on raw material information. Both first principles and empirical models can be used for feed forward control. Given the measured deviation of the incoming material properties from the target value, the feed forward control adjusts the process conditions to achieve the desired output.

Kourti[9] presented a feed forward scheme utilizing multivariate projection space for a pharmaceutical product. That example illustrates a feed forward control scheme for Unit N based on input information on the "state-of-the-intermediate product" from unit N-1. The settings for Unit N are calculated and adjusted such that the target value for Quality Y is met. A multivariate model was built to relate the product quality to the process parameters of unit N and to the "state-of-the-intermediate product" from Unit N-1. The "state of the intermediate product" is a multivariate projection of all the deviations of the raw materials and the process parameters up to unit N-1. From this model, a quantitative understanding was developed showing how process parameters in N and the "state-of-the-intermediate product" from N-1 interact to affect quality. This example is illustrated later in this article, in the Example of Models in QbD section, example 2.

Real Time Batch Process Control

Real time control of product quality in a batch process can be attained using the simultaneous on-line adjustment of several manipulated variable trajectories such as temperature, material feed rates, etc. Traditional approaches, based on detailed theoretical models are typically based on nonlinear differential geometric control or on-line optimization. Many of the schemes suggested in the literature require substantial model knowledge or are computationally intensive and therefore difficult to implement in practice. Empirical modelling offers the advantage of easy model building.

Empirical models utilizing latent variable methods have been applied to control product quality in batch processes. A multivariate empirical model predictive control strategy (Latent Variable Model Predictive Control (LV-MPC)) for trajectory tracking and disturbance rejection for batch processes based on dynamic Principal Component Analysis (PCA) models of the batch processes has been presented[13] This model can be applied for drying, granulation, and other batch pharmaceutical processes.

Setting Multivariate Specifications on Raw Material for Quality Control

Duchesne and MacGregor[10] presented a methodology for establishing multivariate specification regions for incoming materials in order to maintain final product quality. Their idea was to control the incoming material variability for a fixed process. Empirical multivariate methods were used to extract information from historical data (where there was causal variability) and to relate the properties of the supplied raw materials and the process variables to the product quality. Additional data can be collected using DOE. The specification regions are multivariate in nature and are defined in the latent variable space. The incoming material is accepted if its properties fall within a multivariate target.

Product Transfer (Scale-Up or Site Transfer)

Scale-up and product transfer to a different site present similar problems in estimating the process operating conditions at a new plant to produce the same product that is currently produced in a different plant.

Both first principles and empirical models have been used in the past in scale-up; the type of model chosen often depends on the first principle understanding of the unit operation in question. A comprehensive example for design and scale-up based on first principles can be found for crystallization in McKeown, et al,[14] Similar examples can be found for other unit operations where first principles are well understood. In other cases, scale-up can be effectively based on empirical DOE based approaches.

An example of first principles model is thermodynamic modelling to predict the changes in temperature and relative humidity accompanying the phase change of a coating solution liquid to vapor. Such a model can allow the process engineer to substantially develop a coating operation design space using computer models prior to experimental confirmation batches. The approach is not only useful in early development, but also can guide scale-up. With a prudent choice of dimensionless parameters, a design space at the small scale can be translated directly to the large scale via this approach. A thermodynamic model for organic aqueous film coating is reported by am Ende and Berchielli,[15] and a working example is provided by am Ende, et al.[16] Phase diagrams can represent a compositional design space that drives to a specific desired phase/outcome; an example of this is crystal form/phase control during drug substance crystallization and drying.

Attempts also have been made to solve scale-up and site transfer problems with empirical models based on latent variables.[17] Historical data with process conditions and other information from both locations are utilized from previous product transfers to aid the transfer of a new product. These data may need to be enriched by a DOE for the current product. The two sites may differ in equipment, number of process variables, locations of sensors, and history of products produced.

Continual Improvement

During the lifecycle of the product, there are many opportunities for improvement in the manufacturing process as more knowledge is gained. Again, modelling can play an important role.

Process validation is defined as the collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.[18] Process validation involves a series of activities taking place over the lifecycle of the product and process. One of these activities is ongoing process verification, the goal of which is the ongoing assurance gained during routine production that the process remains in a state of control (the validated state) during commercial manufacture. In continued process verification, information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality product within commercial manufacturing conditions.

One way to demonstrate consistent production is to utilize Multivariate Statistical Process Control (MSPC). MSPC can provide a monitoring scheme to check that: (1) the process is in a state of control, (2) there is no causal variability in the process, and (3) the observed variability is within the limits of common cause variation. The monitoring scheme usually covers process variables from several unit operations as well as properties of raw materials and quality (both final and intermediate). For example, MSPC on all quality properties would detect if there is a drift in quality whereas MSPC on process parameters and attributes would detect a drift in the process and facilitate diagnosis as to the cause of the drift. When developing empirical models for process monitoring, it is important to consider all pertinent attributes and process measurements taking into account findings from the risk assessment.

MSPC models are empirical, based on historical data. MSPC charts may be constructed using measured variables directly (e.g., Multivariate Hotelling's T^2, multivariate exponentially weighted moving average) or using latent variable methods. In both cases, measured variables may be used as they are or transformed by utilizing previous knowledge (e.g., using meaningful transformations like logarithmic and inverse, using ratios of variables, or other calculated variables). A detailed discussion on these approaches can be found in article by Kourti.[19] When properly constructed, MSPC models can often detect abnormal events such as unusual variability caused by unknown disturbances and pending equipment failure. Two of the authors have presented examples from their respective companies in conferences, where unusual variability in auxiliary process parameters indicated impending equipment failure, such as from a kink on a flexible tube or partial plugged pipes.

It should be noted that MSPC is intended to detect variability that is causal; in other words, it is supposed to ensure that the process remains near the target operating condition. Therefore, when developing a multivariate model for MSPC, the model should be derived using batches manufactured only at the target process operating conditions and producing good product. To test the ability of MSPC models to detect unusual behavior, batches with known unusual behavior should be used as test sets.

It may seem counter intuitive to develop a model limited to a target operating condition, especially since development of a design space is intended to allow more flexible operation. It may be possible to create a common monitoring scheme that applies anywhere in the design space (not

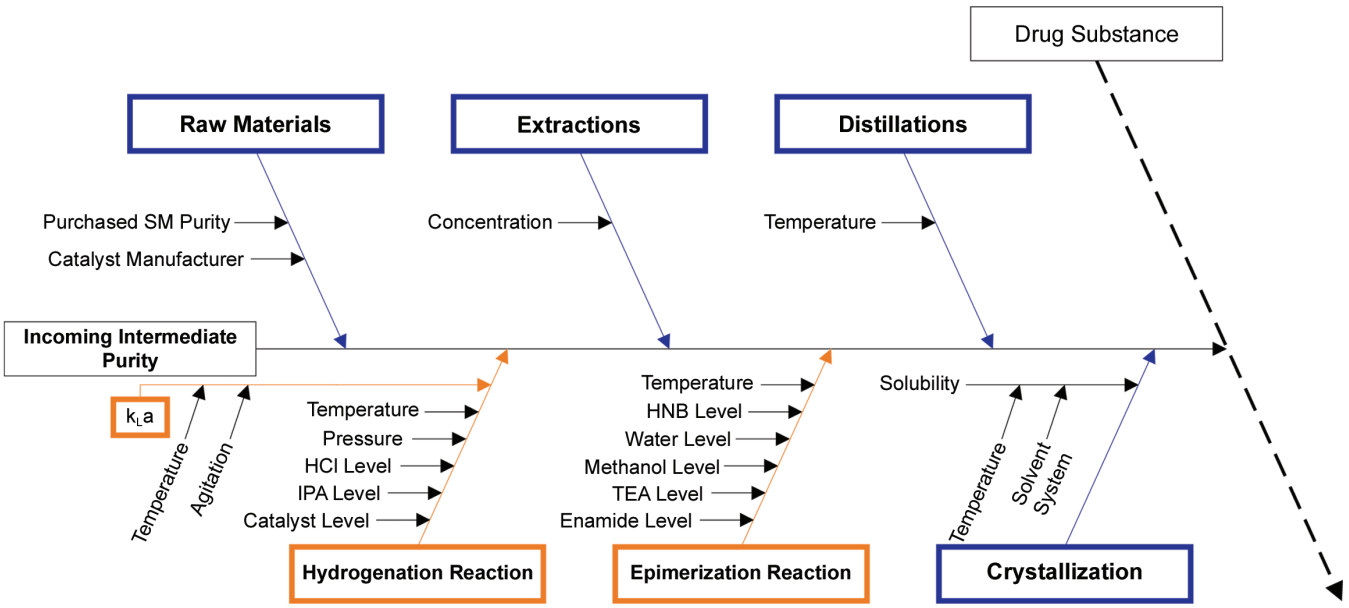

Figure 5. Ishikawa Diagram describing multiple unit operations contributing to drug substance attributes. The abbreviations in this figure are as follows: SM = Starting Material, K_LA: Measure of liquid/gas mass transfer at phase interface, HCl, IPA, HNB, and TEA are all specific reagents.

just the typical operating region); one of the ways to achieve this is by proper pre-processing of the data that enter the MSPC scheme.[19] Alternatively, the MSPC model can be redeveloped upon movement within design space to a new target condition.

In the product lifecycle, empirical models also may be used to analyze historical data for troubleshooting during investigations. Multivariate projection methods may be used that are extremely powerful for such purposes.[9] Much experience may be gained from historical process performance that can be utilized for process improvement.

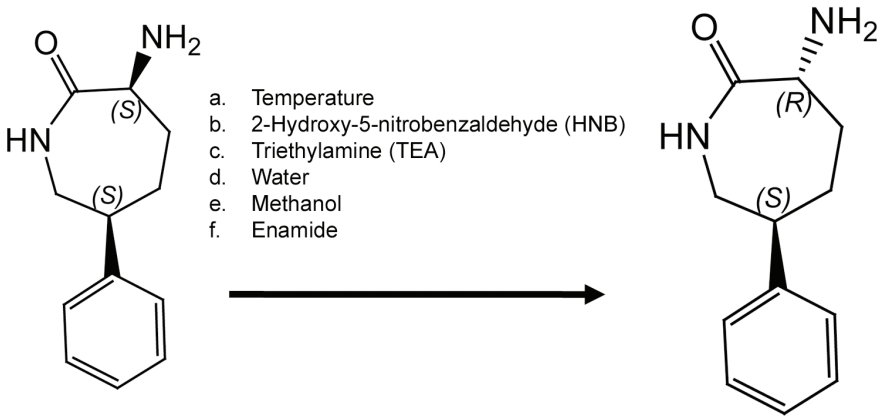

Figure 6. Representative structures of cis (at left) and trans (at right) diasteromers.

Examples of Models in QbD Framework

Example 1: Mechanistic Model of an Epimerization Reaction

This example summarizes an experimental program intended to achieve a mechanistic understanding for an epimerization reaction used to produce a key building block of a drug substance molecule. The methodology is based on using a combination of risk assessment, mechanistic, empirical and statistical approaches to develop a robust design space. Prior knowledge coming into this study includes the reaction mechanism, potential reaction pathways, and a risk assessment of what attributes in drug substance may be important to understand.

This information was used to develop an Ishikawa (fishbone) diagram, which provides a good linkage of desired attributes with the parameters that may influence product quality. In Figure 5, blue boxes were understood to not have interactions with other factors. In these cases, explorative experiments were conducted to achieve process understanding, and where there was uncertainty about the determination, DOE was used to confirm the absence of interactions. The orange boxes were determined to have variables with a significant potential to interact, and in these cases, DOE was used to achieve greater process understanding.

The remainder of this discussion focuses on the epimerization reaction. The epimerization changes the stereocenter on the primary amine in the reaction scheme shown in Figure 6. It is important to control the cis starting material, so reaction conversion requires thorough understanding. Further, downstream processing requires a cis:trans ratio of 19 or higher in order to achieve target purity and main-

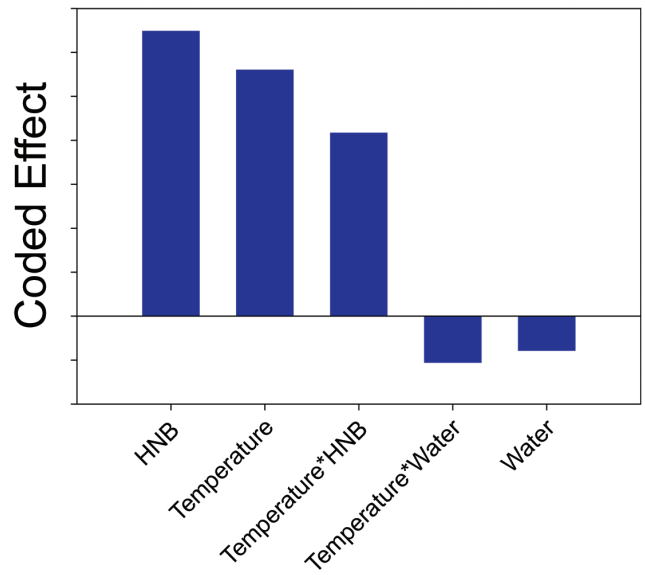

Figure 7. Sensitivity diagram for coupling reaction.

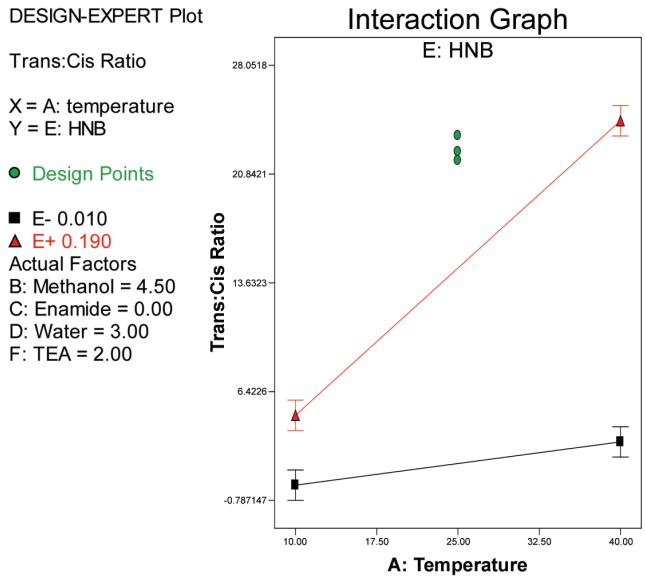

Figure 8. Statistical analysis of conversion data set.

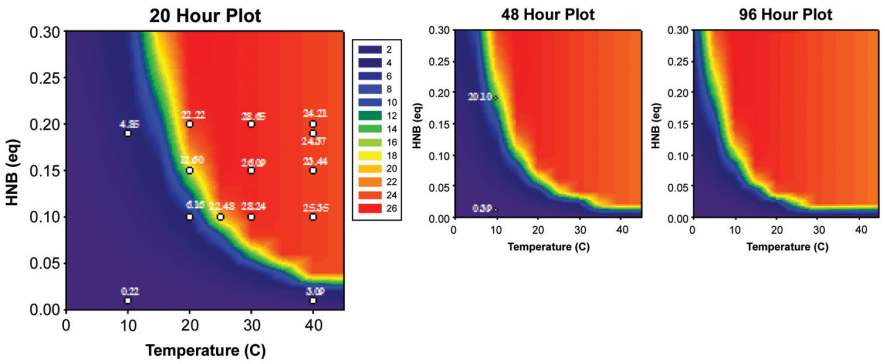

Figure 9. Prediction of reaction completion time as function of HNB and temperature.

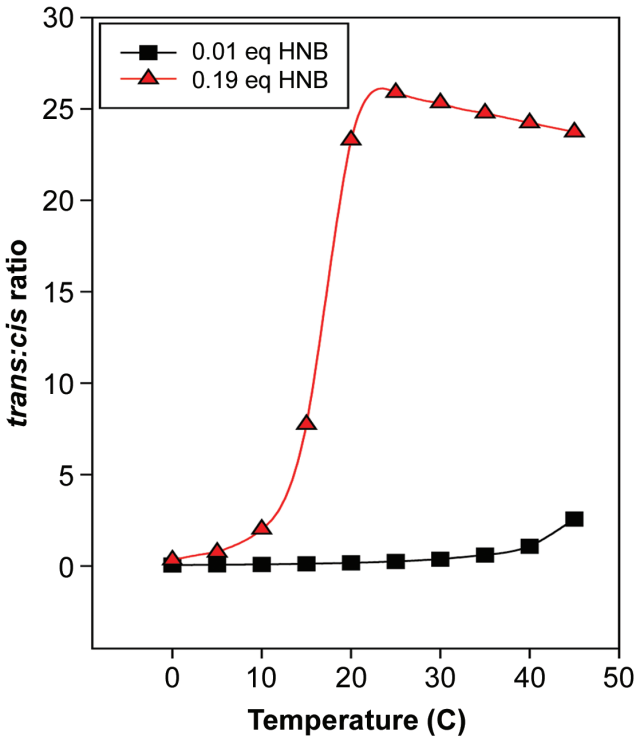

Figure 10. Application of chemical kinetic model to conversion data set.

tain target productivity. The conditions in the downstream crystallization of the final intermediate can be tuned to accommodate variable cis:trans ratios, but 19 was chosen as a minimum optimal point for productivity purposes. Factors influencing reaction outcome are also shown in the Figure 6.

The sensitivity analysis was conducted via a 2^{6-2} (1/4 fraction) factorial design with three center points (19 total runs) to study the epimerization. The ranges selected for testing were informed by prior experience with the reaction (i.e., proven acceptable ranges) with the interest in providing maximum manufacturing flexibility. The results are shown in Figure 7. Note that in this case, HNB and temperature were identified as the most significant factors.

Further analysis and efforts to fit the statistical model with reaction data (including center oints) showed that there was significant curvature in the model - *Figure 8*. The analysis of the temperature as a variable revealed significant non-linearity, as the predicted behavior (see trend lines in Figure 8) did not align with the data observed (see individual data points in Figure 8). Given that temperature was a significant factor, and that chemical reaction theory holds that reactions run at lower temperatures require longer periods of time to achieve equilibrium, the curvature was hypothesized to be a consequence of the time-temperature effect on conversion. Note that the DOE could have been established using criteria that could have addressed the curvature issue; however, an alternative course was taken here as an illustration of how first principles and DOE can be used in combination.

In this case, a chemical kinetics model was designed and fit with commercially available kinetic modelling software. This model initiated on first principles allowed explanation of the time temperature issue noted above:

$$[Cis] + [HNB] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Cis + HNB] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [Trans + HNB] \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Trans] + [HNB]$$

The revised model in Figure 9 showed excellent agreement with the data, and was found to be capable of extrapolating to analyze different reaction time endpoints.

Figure 10 shows a plot of this new information in the same format as the interaction graph shown above; much better agreement with the experimental data and a much better curve fit is obtained.

As a result of the refined model shown in Figure 11, the epimerization factors HNB stoichiometry and temperature were constrained in order to ensure sufficient conversion

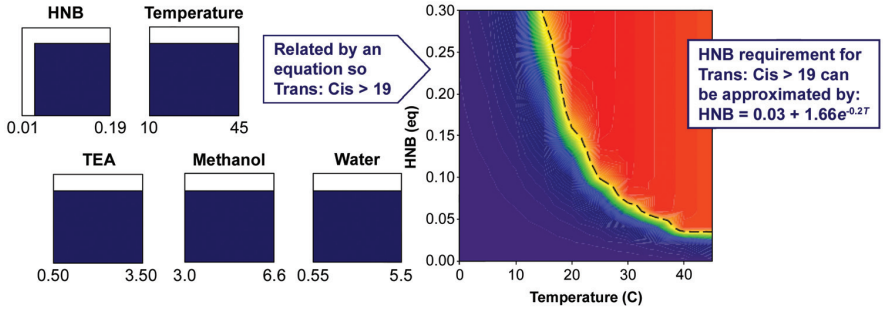

Figure 11. Design space for reaction parameters.

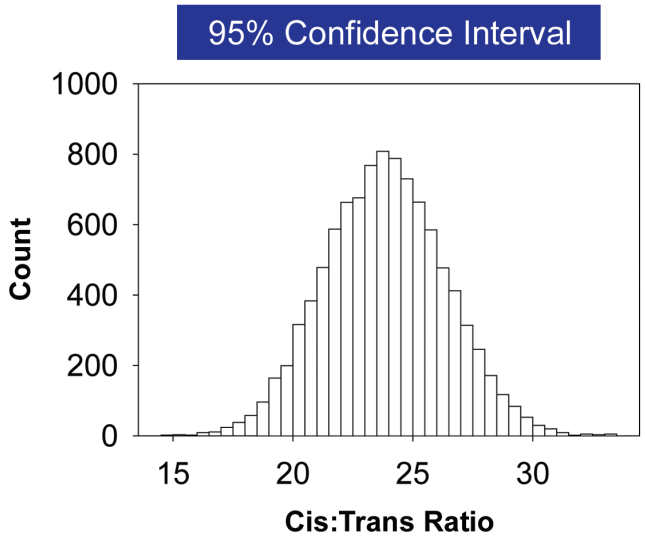

Figure 12. Prediction of cis:trans outcome from Monte Carlo analysis.

while retaining the standard high productivity crystallization and rejecting remaining incorrect diastereomers.

The number of lots produced in support of acquisition of process knowledge, combined with support of clinical studies is typically too small to generate error bars in the traditional sense. This limited data was compensated for by running Monte-Carlo simulations over the proposed design space. The inputs included the distributions from the DOE data combined with random noise around the DOE model. The simulations aligned very well with pilot scale and early manufacturing scale lots, and it was concluded that the process as designed will achieve the target cis:trans ratio of 19:1 with no special adjustments. Figure 12 shows the range of outcomes from the simulation.

Example 2: Feed Forward Control Based on Latent Variables

The next example demonstrates the use of feed forward control action within a design space. A model that describes the design space for the entire tablet manufacturing process as shown in Figure 13 can be derived by relating quality to both the raw material properties and the process parameters of the unit operations. Figure 13 depicts a database where each row represents a batch and the corresponding columns include the process conditions and quality experienced by the material as it is processed through the units. The empirical models derived are causal and based on carefully Design of Experiments (DOE). Such modeling provides flexibility in the control strategy, because it allows for real time adjustments within the design space.

Figure 14 illustrates a feed forward control scheme for Unit N based on input information on the "state-of-the-intermediate product" from unit N-1. The settings are calculated and adjusted such that the target value for Quality Y is met. A multivariate model was built to relate product quality to the process parameters of unit N and the "state-of-the-intermediate product" from Unit N-1. From this model, a quantitative understanding was developed showing how process parameters in N and the state-of-the-intermediate product from N-1 interact to affect quality. Using multivariate analysis assures that the multivariate nature of quality is respected. In this case, the five batches that project in an area within the red circle (two blue batches and three green) have the same state of intermediate product – meaning that

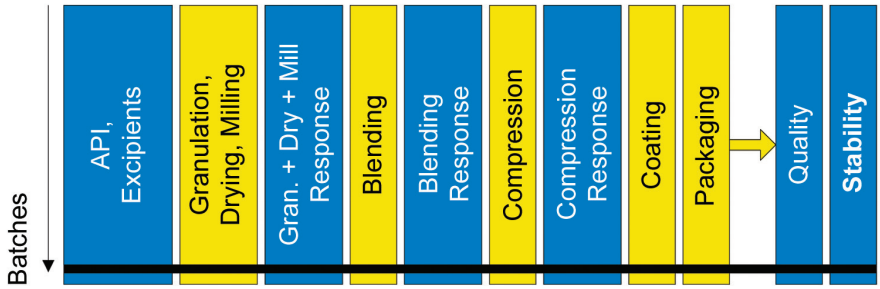

Figure 13. Layout of database for an integrated design space.

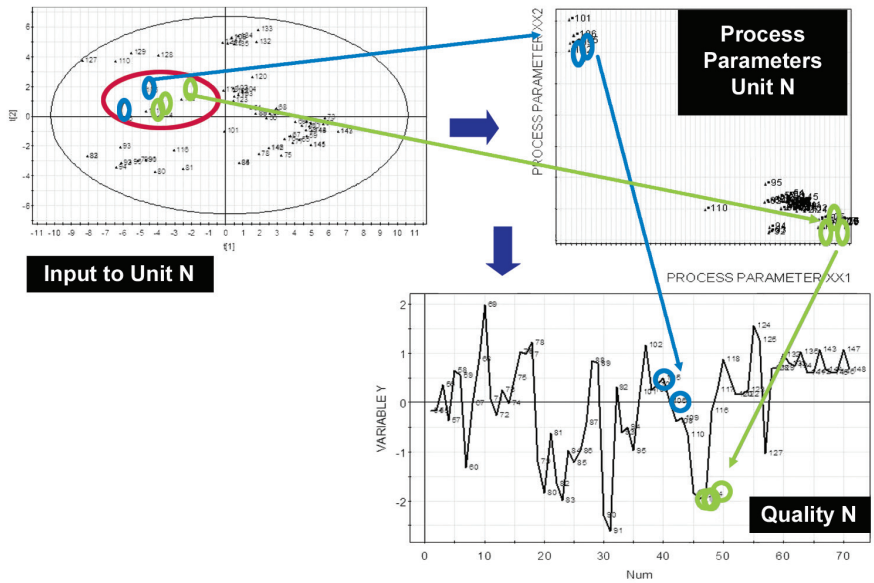

Figure 14. Feed forward control action using information from multivariate projection space.[9] (Reprinted with permission of John Wiley & Sons, Inc.)

up to that time the five batches experienced same raw material and processing conditions. The green batches, when processed with typical operating conditions in Unit N, marked green, resulted in quality below average. By taking a feed forward action and processing them with different operating conditions, marked blue, in unit N, the quality improves with values above average.

Example 3: Multivariate Process Control Applied to a Granulation Process

In Figure 15, MSPC was applied to a high shear wet granulation process. The granulation process consists of different phases, of which only the quality relevant parameters were considered for modeling. The four phases taken into account for modeling were:

1. Pre-mixing: the dry powder is stirred for a fixed period of time.
2. Water addition: the binding solution is continuously transferred to the granulation vessel.
3. Rinsing water addition: the rinsing water is transferred to the vessel.
4. Kneading: the granulate is kneaded for a fixed time.

Different process variable were included into the model, which can be divided into the following different categories:

1. Speed of stirrer and chopper
2. Power consumption, torque and temperature of the granulate
3. The properties of the pump and the addition rate
4. Environmental condition as atmospheric pressure and bowl temperature

The aim of MSPC is to capture the current state of the process and to recognize whether there is a tendency to deviate from typical behavior, in a statistical sense.

Figure 15 shows a latent variable, in this case the score of the first principle component derived from multivariate analysis (PCA) of process data, displayed as a function of time. The alert limits highlighted in red are set at average score ±3 standard deviations at each time point. In this particular case, it was deemed that the first principle component is sufficient to detect atypical process behavior.

By the formation of a process signature, the process dynamics and variability can readily be visualized. For instance, while the dry mixing phase is a static process, the solution addition phase shows a linear increase of the average score over time. Furthermore, the variability at the start and end of a phase is more pronounced than the middle of the phases.

The MSPC charts described in this example are one of the alternative ways of creating and presenting monitoring charts for batch processes. A detailed discussion of the analysis and MSPC of batch processes and the available methodologies as well as the advantages and disadvantages of certain approaches, can be found in the Kourti[19] and Wold, et al,[20] articles.

The Lifecycle of a Model in a Production Environment

As evident from the section on Overview of Models, differ-

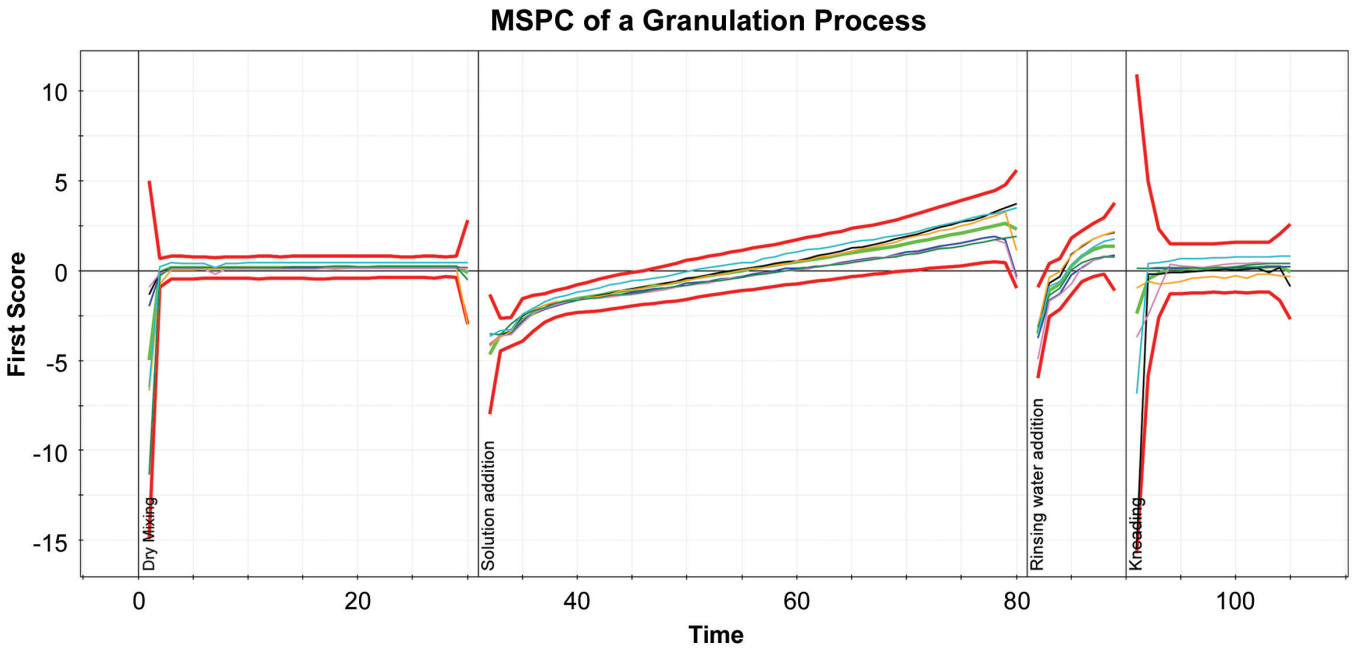

Figure 15. Assessment of different granulation batches as a function of time in different phases by a MSPC model.

ent types of models are used at various stages of the lifecycle of the product, from product development to scale-up, and through continual improvement. Each model has its own lifecycle, depending on the function it performs. The development of the model is just the beginning of its lifecycle. The validity of the model should be ascertained during its lifecycle, from development to external validation and during implementation, with the rigor of the activity being commensurate with the purpose of the model. The implementation of models in a production environment inherently has a number of challenges and obstacles which should be anticipated prior to their efficient and successful application. For models that support PAT for example, achieving a sufficient predictive performance with the given constraints of the eligible methodology is one of the challenges. Beside the scientific constraints, the methods have to be validated to demonstrate that they are comparable with conventional methods usually performed on the finished product in the Quality Control (QC) labs. The general need for the validation of these process models stems from the fact that the information and outputs retrieved from the model will be used for quality decisions to release the product.

The lifecycle of a model involves the following steps which are iterated as necessary:

- Model development
- Model validation (includes internal and external validation)
- Model implementation
  - Comparing real time results with the reference method; this is referred sometimes as Parallel Testing Phase.
  - Release for usage
  - Model maintenance (which may necessitate model update)

The phase prior to the real time implementation phase is often referred to by other industries as the *"off-line phase."* The following statement relates to the implementation of multivariate statistical models: *"The off-line phase of development is essentially the work done to determine the feasibility of meeting business objectives through the application of Multivariate Statistics (MVS) technologies. The off-line phase can be broken down into the following tasks: data selection and preparation, model development, and evaluation. Each step is done keeping in mind the original objectives and incorporating as much knowledge of the process as possible."*[21]

Model Development

Model development typically includes the steps listed below. These steps are usually executed in a sequential manner, but often it may be necessary to return to an earlier step, thus imparting an iterative nature to this process. The general steps to consider for model development are:

a. Defining the purpose/objective of the model and the acceptance criteria.
b. Deciding on the type of modelling approach (e.g., first principles, mechanistic, empirical, or hybrid) and experimental/sampling methodology to support the model's development.
c. Defining the variables to include in the model, which can be based on risk assessment, scientific and process knowledge and experience.
d. Understanding the limitations of the model assumptions in order to correctly design experiments, to interpret the model results, and to help develop appropriate risk mitigation strategies.
e. Collecting experimental data to support the model development. These data may be collected at development scale or at commercial scale, depending on the nature of the model. Since the performance of the model is contingent on the quality of the data that was used to derive the model, it is important to ensure that appropriate data is used for model building.
f. Defining any pre-processing of the data or variable transformations. For example, for MSPC models for a jacketed reactor, rather than using variables like the input (T_{in}) and output (T_{out}) temperatures and the flow (F) of the cooling liquid, one may use the calculated variable ($T_{in} - T_{out}$) * F which is related to the heat content and should not exhibit seasonal fluctuation like the temperatures.
g. Developing models, based on the scientific understanding, the collected experimental data, and the objectives of the model.
h. Assessing the validity of the model with internal metrics and external validation, as applicable, prior to implementation. Validation metrics are discussed in detail in the next section. This stage typically includes assessing potential limitations, risks gaps and mitigations. Risk analysis can be used to set thresholds of methods and acceptance criteria for validation. Other points to consider at this stage are:
   - **Uncertainty:** for both mechanistic and empirical models, significant uncertainty may exist in the model predictions, due to the following reasons: (a) underlying assumptions and simplifications used in model derivation, (b) variability (noise) in measurements and (c) error in the model fit. When developing models, it is important to evaluate the uncertainty in the model, assess what uncertainty the model can tolerate and then define an approach to mitigate the risks imparted by the uncertainty. For example, 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.

- **Range of Variables:** ideally, the range of variation of parameters for model development and validation should be representative of the expected range of variation of these parameters during model implementation (e.g., conditions that would generally be expected during operation including the variability anticipated in future production). The importance of the range of variables for data based models has been stressed by practitioners in other industries. *"In the case of a predictive model, the training set should span the operating space in a balanced way. Balancing the way data are collected requires care to ensure that certain regions in the operating space are not over or under represented in the training set in the overall set of observations. The number of observations to be taken from a particular region of the operating window will vary depending on the application."*[21]

i. Documenting model results including initial assumptions and plans for transfer to commercial scale and maintenance and update of the model throughout its life cycle, as applicable. Model maintenance considerations are imperative for high impact models. The level of documentation depends on the impact of the model, as is discussed later.

Scale-Up and Transfer Considerations

When the objective is to implement a model that was developed at pilot or laboratory scale to commercial scale or to transfer a PAT calibration model to another instrument, the scale-up/transfer issues may be addressed in one or more of the following ways:

Scale-Up of Design Space Models: a scale-up approach can include, but is not limited to:

- Using appropriate scale-up correlations
- Defining a model in terms of scale invariant or dimensionless parameters
- Implementing an enhanced monitoring/testing scheme of sufficient duration to verify the quality of product manufactured when moving to areas of design space not previously verified at commercial scale.

PAT Models: A calibration model developed at the laboratory instrument and process equipment should be verified when transferring to the commercial scale. For situations where commercial conditions cannot be simulated in laboratory or pilot scale data, the method should be developed based on full scale data.

Model Validation

In general, validity of a model's performance needs to be established prior to its implementation for decision making purposes. The goal of validation, whether it is applied to a process or an analytical method, is to demonstrate that the process or the method is suitable for its intended use in the intended process conditions and scale. In this section, the concept of validating models will be discussed, highlighting the different aspects to be considered. Data considerations for model development and validation are also discussed.

Considerations for first principle models, or phenomenological models, follow a similar thought process to that developed for empirical modelling, but with a number of major distinctions. When a system can be described accurately with existing tools that exemplify thermodynamic and rate phenomena, those tools can usually be successfully leveraged to describe the system. As a consequence, these models would not typically require the same level of validation as an empirical model. Often, there is no basis for using an independent data set, as the verification has been done through the prior knowledge and widespread use. Thermodynamic functions are state based, and as a result, tend to be path independent.

As an example, in drug substance processes, equilibrium process conditions are widespread. A phase diagram describing crystal form as a function of composition or temperature is a classic case. The model is developed based on existing equilibrium theory. During model development, the model is often tested at extreme conditions, to evaluate its response to such conditions; however, once developed, the model would be expected to behave consistently across scales given compositional control within the range shown to deliver the desired crystal form. A similar case is the use of kinetic models, which by their nature relate system concentrations, temperature and time and more.

Internal Validation

In the development phase, after the model generation, internal validation assessment is typically carried out to verify the performance of the model. The model prediction is compared to actual values with data available at the time of method development.

The data set used for model generation is referred to as the *Calibration Set or Model Building Set or Training Set*.[21] This set should include the variability anticipated in future routine production and is representative of the commercial process (e.g., equipment, steps). When the model is used for prediction of a property (i.e., water content or assay), data covering the expected range of variability should be used. When the model will be used for MSPC (that is, to detect variability beyond common cause variation), only data of compliant batches which are representative of typical operating conditions should be used to define the control limits.

The data used for verifying the model performance during the development form the *Internal Validation or Test*

Set. The confirmation of the model by these data is referred to as internal validation. These data are excluded from the dataset available for modelling and are used as an independent data set for a confirmation of the model with respect to accuracy and robustness. For some processes, there may not be sufficient data available to exclude them from the data set for model building since all data are needed for establishing the model. In this case, techniques such as cross validation, random (Monte Carlo) re-sampling, or boot strapping[22] can be used.

For mechanistic models, when DOE are performed for the calculation of constants or coefficients, internal validation also should be performed.

External Validation

External validation is performed with an independent data set after the model is completed and fixed. This data set, called *External Validation Set or Validation Set,* contains data that were not used to build the model. Verification of the model with an appropriate dataset is especially important to demonstrate robustness - *Figure 16*.

The experimental procedures, parameters to be validated, and acceptance criteria that must be met should be defined in advance. In a compliant environment, they are typically defined in a validation written protocol, issued prior to the execution of the validation, and maintained within the firm's quality system. Since the model physically exists in the form of the digital data, the model and the related data methods are typically "locked" before external validation to prevent any modification of the methods.

The amount and type of data that should be included in the external validation set depends on the model that is validated. The user should consider both the number of batches required and the range of variation that will be covered. A predictive model that is expected to be valid for the entire design space could be tested with bracketed studies or by covering higher risk areas. For a statistical process control model, the model's ability to detect abnormal situations should be part of the external validation, along with checking that the model is correctly compliant and representative of the batches being manufactured. Unless abnormal situations have actually occurred and data exist that can be utilised to test the model, disturbances may be "altered artificially" to create such cases. This can be achieved by creating off-line artificially altered process data to investigate if the model detects the deviations.

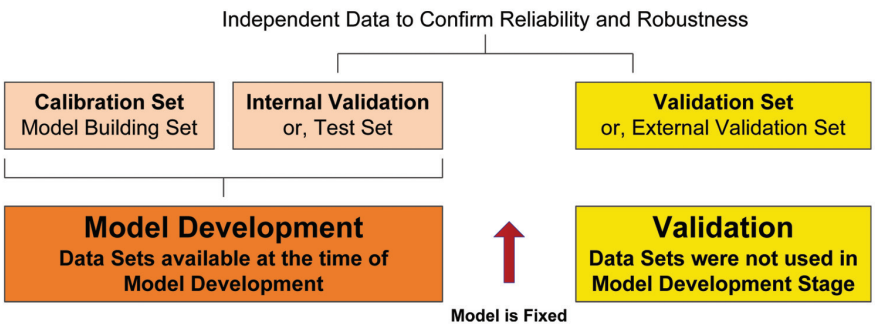

Figure 16. Categories of data involved in development and validation phase.

Validation Parameters and Acceptance Criteria

In general, the validation parameters and the related acceptance criteria strongly depend on the intended purpose and scope of the model. For predictive models of quality attributes, the acceptance criteria depend on the predicted quality attribute and should be defined as part of the established validation procedures and control strategy associated with a thorough risk analysis. For example, the acceptable difference between the model prediction and the values resulting from an analytical measurement could be different for a dissolution model (with higher inherent method variability) than for an assay model. Examples of acceptance criteria for validation of empirical qualitative and quantitative models are given in Table A.

Qualitative Models or Pass/Fail Models

These are models where certain estimated "metrics" are tested against limits. This category includes, but it is not limited to 1. MSPC models, where metrics like Scores, Hotelling's T^2 or the Residuals (DmodX or Squared Prediction Error-SPE) are checked against limits,[9] 2. models like the Caterpillar Algorithm for blending end point detection[12] where end point has been achieved provided that a metric falls within limits, and 3. identification models. For qualitative or pass/fail models, specificity and robustness are the main parameters to be confirmed and tested. Compliant batches should fall within the defined threshold or control limits of the specific metrics of the model.

The robustness for MSPC models used for process monitoring can be assessed by evaluating the performance during a longer period of time where it is observed how the model is coping with the natural variability of the process. For these models it should be demonstrated that they are capable of flagging batches that are outside the range of previous typical operation. For these types of models, robustness test typically cannot be designed at the time of launch and set up due to financial impact of producing batches under non normal conditions. It is possible sometimes to test the capability of flagging abnormalities, by deliberately configuring process data off -line to simulate a process deviation. The outcome when these data are applied to the model can then be evaluated. For NIR models,

robustness can be tested during development by varying different measuring conditions, operators, presentation to the probe.

Quantitative Models or Predictive Models

For quantitative models (e.g., predicting potency of a tablet using NIR or predicting dissolution), the accuracy can be determined by comparing the predicted values to the reference method. The prediction error of the model should be comparable to the reproducibility of the reference analytical method. For the assessment of linearity, the accuracy (e.g., the bias to the reference) over the expected range and the random distribution of the residuals within a defined bandwidth are reliable indicators. As part of the proof of specificity, the ability to avoid false positive results can be demonstrated. A test is often performed to assess whether the new point belongs to the same population as the points used to develop the model; this is done by assuring that both Hotelling's T^2 and DModX (or SPE) of new point are within limits. The idea behind this approach is that the outlier diagnostics, which are used as a filter prior to the application of the model, are specific enough to detect/discriminate data which are atypical compared to the data which were used for modeling and which are representative. If these diagnostics are detecting something unusal, e.g., in the form of Hotteling's T^2, SPE, the model should not be applied in order to avoid false positive or false negative results. In analytical testing in the lab, this is usually performed using special samples either spiked or adjusted to a specific concentration. For a process model applied on-line in production, this is less feasible due to financial restriction of manufacturing non-compliant material.

For mechanistic models, the extent of testing would be expected to be consistent with the parameter/attribute being modelled and the importance of the model. For example, reaction rate, phase diagram, distribution coefficient, all would have different metric and acceptance criteria.

The robustness and stability of the model can be assessed by having a sufficient number of data available, which were produced over a longer period of time covering anticipated variability in environmental and process condition, e.g., different batches of incoming material and seasonal changes in air humidity. Another way could be to assess the impact of potential factors identified previously in the frame of a risk

EXAMPLES OF QUALITATIVE MODEL VALIDATION		
Validation Parameter	Specific Metrics	Acceptance/Rejection Principles
Specificity/Selectivity	Membership criterion, e.g. Hotelling's T2 or Residual analysis	Points falling within predefined limits are accepted Points falling out of limits are further analysed for their root cause
Robustness	Number of batches, over a certain period of time, large enough to cover typical variability related to raw materials, environmental and process influences	Batches exhibiting the typical common cause variation of the process are accepted by the model

EXAMPLES OF QUANTITATIVE MODEL VALIDATION		
Validation Parameter	Specific Metrics	Acceptance/Rejection Principles
Selectivity/Specificity	Testing Model Applicability: check that the new data come from the same population as those used to develop and validate the model.	Batches that reveal an unusual situation or are not produced at expected normal operating conditions are flagged and filtered out prior to quantification
Accuracy	Root Mean Squared Error of Prediction (RMSEP/ BIAS to the reference method)	Comparable to established acceptance criteria for conventional method transfers taking the inherent precision of the two methods, (i.e. the model and the reference into account).
Linearity	1. Distribution of residuals 2. Accuracy across the range	1. Are randomly distributed 2. Residuals stay within a defined bandwidth over the complete range
Precision	Repeatability Reproducibility	For batch model, sometimes repeatability or reproducibility is not possible to measure as a batch is unique and multiple measurements are not feasible
Robustness	Number of batches over a certain period of time covering environmental and process variability (e.g. different raw material batches)	Batches exhibiting the normal variability of the process are accepted by the model with no impact on the predictive performance

Table A. Examples of acceptance criteria for validation of empirical qualitative and quantitative models.

assessment on the performance of the model using DoEs.

Implementation Phase

Subsequent to validation, the model is integrated into the company's quality systems and there is on-going evaluation as part of regular maintenance. For example, the implementation of a high impact model in a production environment consists of verification at production scale phase, release for usage and maintenance phase.

Verification at Production Scale Environment

In this phase of production scale verification, the model output is assessed against traditional testing of quality to ensure that it can perform as intended in a production environment. The need and extent of the production scale verification depends on the variation covered during validation in the intended production conditions and scale. The range covered and the batches required for this purpose depends on the type and purpose of model. This testing phase enlarges the body of data in order to make a statistical assessment of model capability prior to the final implementation. For predictive models, this approach includes comparison of the models prediction with the reference method. For MSPC models, the ability to differentiate between typical and abnormal situations is tested. For process control models (e.g., feed forward/feedback), this phase makes sure that process control algorithms and procedures deliver the required outcome.

For predictive models, companies often choose to test at or near the target operating conditions at this stage. Alternatively, it is also possible to evaluate systematic variation within the design space. If testing of the model occurs only at target processing conditions, a procedure could be included within the production quality system to help assure that the model performs as desired when there is variation (planned and unplanned) in the processing conditions. Some tools that could be used are: MSPC to detect unplanned disturbances and risk assessment to assess performance in planned disturbances (e.g., change of raw material).

MSPC models can and should[9] be tested off line prior to real time implementation, by utilizing process data to assess Type I and Type II errors and to make decisions about real time implementation.

Release for Usage

Once the model is released, it is used as an element in the GMP system, that warrants routine maintenance.

Model Maintenance

After the model is released for usage, the model is generally checked periodically based on certain criteria, as discussed later in in the *Maintenance Model* section of this article.

Usage, Incident and Change Management Considerations

After the validation of the model, procedures for its implementation within the production system should be considered; that is, how to incorporate and integrate the model into the control procedures and release flow of the quality systems. These procedures typically encompass the definition of process flow, incident and change management, and define what is seen as an out of control incident. For these procedures, it is suggested to include a clear definition of thresholds and control limits. One possible outcome of an incident might be that the applied model is not covering the present variability which could entail an update of the model.

Usage and Implementation

For the application of a model in production, the automated data flow between sensors, the model and the distributed control system is highly essential for a compliant and secure usage. The control metrics and logic should be clearly defined and embedded into the manufacturing recipes. Based on method specific parameters, a warning can be automatically generated if a certain control limit or threshold is exceeded. Examples for such deviations could include a certain critical process parameter, latent sum variable (as a score) or a residual deviated out of the predefined acceptable ranges. Furthermore, fall back scenarios can be in place in case that the data flow might break down, e.g., in case of a sensor failure or a breakage of a data connection or server. Ideally, procedures would be in place to handle such unplanned incidents in a systematic pre-planned manner. In particular, for multivariate models, the event of having partially missing data could automatically generate alerts to the process expert who can then react.

Incident Management

For applying models in the production environment, clear procedures for the usage should be established including defining what is seen as an "unusual event." In MSPC language, an "unusual event" occurs if operation falls outside typical limits, and may need to be analyzed further; this does not necessarily mean a bad product. A clear definition of thresholds and control limit can be developed in combination with a thorough risk assessment.

In the case of an "unusual event," the incident is usually checked to assess whether this finding is being escalated to real process deviation and whether/when QA needs be informed. The investigation typically includes a thorough examination of all process steps involved, equipment and sensors and personnel engaged to trace back the incident to the root cause of the model out of trend occurrence. In particular, a QC testing plan for the involved material might be considered.

One possible outcome of the incident might be that the applied model is not covering the present variability. This scenario would typically entail an update of the model.

Maintenance of Models

Typically, models are evaluated periodically and may need to be updated due to an instrument or process drift. Additionally, unaccounted variability (e.g., changes in raw material) could result in out-of-spec predictions from the model. It is important to monitor the performance of the model over the lifecycle of the product as well as to monitor that the assumptions of the model still hold. An approach for monitoring model performance can include periodic comparison of model prediction with a reference method. Early identification of model defects allows making adjustments to the model (e.g., recalibration) before failures occur.

For data based models, maintenance has already been discussed as a crucial stage in the model lifecycle in the literature. *"Continued evaluation of system performance relative to project objectives and the actions taken to ensure ongoing performance are part of system maintenance. Maintenance can encompass many activities including the updating of model parameters and control chart limits. Various methods can be used to maintain model parameters and control limits. These methods can include periodic off-line rebuilding of models, the development of automated model updating methods, or some combination of these activities. In either case, the goal is to ensure that the empirical models used in MVS analysis retain a high degree of fidelity to the process so that client needs continue to be met.[21] Having long-term maintenance strategies in place is important in ensuring continuing success."*

"Once a model has been developed, it is often the case that the tacit assumptions underlying its validity are forgotten or neglected." A discussion on model validation and detection of parameter changes under closed-loop conditions can be found in Jiang, et al, (2009).[23]

Empirical process models can be re-evaluated at defined intervals as part of an ongoing method evaluation throughout the life cycle of the model and the associated process. The main focuses of planned assessments are:

- A reassessment of the accuracy of the method including a comparison with the reference method (e.g., repeat certain parts of the validation)
- Statistical assessment of performance of the model (similar to Annual Performance Review (APR)/Product Quality Review (PQR))
- List of all deviations encountered in the evaluation period
- Final assessment of the validity of the method and statement about the necessity of a model update

The outcome of the method reassessment under regular method maintenance is the conclusion whether the performance of the model is still appropriate and accurate to support further use of the model. If the performance is inacceptable, corrective actions should be taken. For example, the model could be developed, taking into account new data, process insight and experience.

The frequency of checking the adequacy of model performance depends on the variability, complexity and the number of batches produced per year. An alternative approach to having a fixed time would be to execute this kind of assessment after a defined number of batches produced, which is similar to the concept of frequency testing.

Other incidents, such as change in a sensor, change in raw material, or change in manufacturing equipment could trigger reassessment of model relevance, potentially followed by a redevelopment and adaptation of the method.

Regulatory Considerations for Model Implementation

Points for consideration for regulatory submissions are discussed in this section. These points are additional to the information that is documented under the firm's quality system. For example, for high impact models, information in the quality system typically includes: development report, validation report, Standard Operating Procedures (SOPs), release process, maintenance, and incident management.

Considerations of Model Related Information in Regulatory Submissions

In accordance with ICH QIWG Points to Consider[5] section on models, the level of detail for describing a model in a regulatory submission is dependent on the impact of its implementation in assuring the quality of the product. Additionally, documentation of model related information in regulatory filings is dependent on the intended use of the model and the risk associated with it. For example, if a MSPC model is used for monitoring only and not for control purposes, it can be regarded as a low impact/risk model. However, an MSPC model used as a part of a RTRT strategy could be considered a high impact model.

The applicant should consider including the following information for various types of models:

I. Low-Impact Models: a discussion of how the models were used to make decisions during process development.

II. Medium-Impact Models:

- Model assumptions
- Tabular or graphical summary of model inputs and outputs
- Relevant model equations (e.g., for mechanistic models) either in the submission or via a reference
- Statistical analysis where appropriate

- Comparison of model prediction with measured data
- Discussion of how the other elements in the control strategy help to mitigate uncertainty in the model, if appropriate

III. High-Impact Models: data and/or prior knowledge (e.g., for established first principles driven models) such as:

- Model assumptions
- Appropriateness of the sample size
- Number and distribution of samples
- Data pre-treatment (e.g., variable transformations, any filtering of the data, spectral pre-treatments)
- Justification for variable selection (wavelength selection for spectral data)
- Model inputs and outputs
- Model equations
- Statistical analysis of data showing fit and prediction ability
- Rationale for setting of model acceptance criteria
- Model validation (internal and external)
- General discussion of approaches for model verification during the lifecycle.

Other considerations in accordance to regional requirements (e.g., EMA 2014a,b)[24,25] could include:

- Describing details about the composition of the data sets used for model development (e.g., number of independent batches that were used, number of samples per batch, criteria used for separating the batches into sets, demonstrating that these datasets are representative of the expected process variability in routine production)
- Procedures for handling outliers
- For chemometric models, the rationale for selection of number of principal components, demonstration of the linkage between the weightings of the variables in the principal components to the process, method of error estimation, Root Mean Square Error of Cross Validation (RMSECV), Root Mean Square Error of Prediction (RMSEP), etc.
- If data from a reference analytical method is used to generate an empirical model, demonstration that the reference method is fit for purpose (e.g., full description and validation of the reference methods).

Considerations for Model Verification

Usually, models are developed with data generated at lab or pilot scale. One of the key points to be discussed in the regulatory submission is the applicability of the model at commercial scale. This can be conveyed by providing evidence of scale independence, available commercial scale data, or by discussing plans for model verification at commercial scale. As already stated above, the level of detail to be provided for model verification depends on the impact of the model on product quality. For example, for a high impact model, such a plan could include the parameters that will be varied, the ranges that will be covered, the CQAs that will be tested, the acceptance criteria, and the number of new independent data that will be used.

Considerations for Maintenance of Models

The approach of model maintenance and update can be designed relative to the importance of the model in the control strategy and its potential to affect product quality. Clear metrics for model update may be established depending on the impact of the model. As discussed earlier, model maintenance information could include the following: risk based frequency of comparing model prediction with the reference method, triggers for model update, and approach for model recalibration. The reporting of model updates is according to regional requirements. Details about model maintenance are documented in the firm's quality system.

Disclaimers

1. By E. Korakianiti: the views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
2. By the rest of the authors: the views expressed in this paper are the personal views of the contributing authors and do not necessarily reflect the official position of their respective organizations.

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