Practical Implications of Quality by Design to Chromatographic Method Development

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Quality by Design (QbD) was first described by Joseph M. Juran[1], and applied heavily, particularly in the automotive industry. The fundamental premise behind QbD is that quality can be "designed in" to processes through systematic implementation of an optimization strategy to establish a thorough understanding of the response of the system quality to given variables, and the use of control strategies to continuously ensure quality. The FDA has recently begun to advocate the QbD methodology for the pharmaceutical sector.[2] There are a number of implications of the concept, including modeling of the influence of values of variables on quality, design of experiments, and ongoing refinement of processes as information is collected. Recently, analytical chemists have begun to advocate the extension of QbD philosophies to the development of analytical methods in addition to the development of manufacturing processes. Some of the concepts are more applicable than others, and some have been advocated by many method development experts for some time, but modern technology has created an opportunity to revisit strategies for creation of chromatographic methods in particular, and it is certainly interesting to investigate the new opportunities in the context of Quality by Design. This article will examine the areas where QbD methodologies can help with method development today, with emphasis on practical implementation and modern technologies.

QbD and Method Development—a Paradox?

At first glance, applying QbD to chromatography can be confusing. This is mainly due to the fact that the ICH guidelines describe optimization of manufacturing processes with the assurance of quality of the final product, i.e., the drug. The chromatographic method can be a contributor to the measurement of quality of the drug, but the optimization of that chromatographic method is not directly part of the development scheme for the pharmaceutical product. When QbD processes are applied to the creation of a chromatographic method, the measurement itself is not a process, but rather the product. The quality of the chromatographic method (and thus the measurement) is the objective in question. As a benefit of the excellent design of the chromatographic method, the quality of the drug product can be measured and proven more effectively, but the design of the chromatographic method can be viewed in isolation, and the measurement itself in essence is the product. Put another way, the quality attributes of the measurement are to be optimised. The goal of QbD in method development is consistent quality of the chromatographic measurement.

The Modern Method Development Toolset

Method development gurus have long advocated systematic approaches to method development, but widespread adoption has eluded them. The majority of chromatographers have depended on a "seat-of-the-pants" approach to the problem. This has led to slower development in many situations, but perhaps more importantly, challenges in validation. At least one of the reasons for the rejection of systematic approaches to development has been associated with the technology available to the chromatographer. However, recent advancements across all aspects of chromatographic method development put chromatographers in the position to exploit the tools at unprecedented levels. There is a "perfect storm" of technology available. Today, it is possible to examine a wide array of chromatographic conditions due to ready access to Ultra High Performance Liquid Chromatography. Parallel screening of columns, buffers, and solvents is possible in light of the fact that scores of injections can be done overnight, for example. Inexpensive, robust mass spectrometry detection, combined with chemometric data reduction, makes it possible to cope with the large amount of data that is produced. Often ignored, but critical in this context is the tremendous computing power now available. Without the RAM, hard drive space, and processing power of modern computers, it would be impossible to consider collecting this amount of data. Similarly, this computational power enables modeling of chromatographic responses. It would be impractical to attempt 4-, 5-, and 6-dimensional optimization of parameters even 5 years ago. Now such systems can be optimised routinely. Finally, the automation of data collection, from both a hardware and software perspective, is available to streamline the data collection and eliminate the transcription errors that are inevitable when manually creating injection sequences. We are now in a position to design chromatographic methods with a rigour never before possible. Quality by Design methodology provides a perfect context to efficiently exploit this rigour.

Quality by Design and Chromatographic Methods

There is no single QbD approach to chromatographic method development, but there are commonalities. A broadly-applicable approach to method development is shown in figure 1. Each step in the process will be considered in turn.

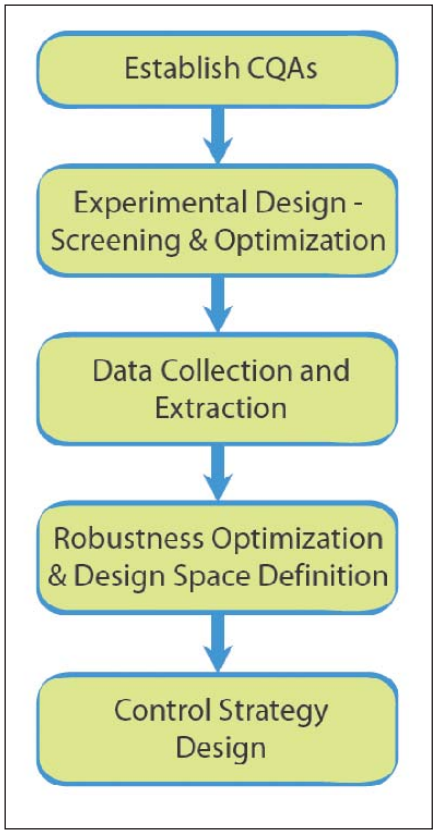

Figure 1. Overview of a QbD Process for Chromatographic Method Development

Software is a critical part of QbD chromatographic method development. There are various method development packages available, including optimization tools such as DryLab[3] and ACD/LC Simulator[4], and automation and experimental design tools such as Fusion AE[5] and ACD/AutoChrom Method Development Suite[4]. The application of these tools will be discussed in the context of the overall method development process below.

Design Space

A goal of Quality by Design is the establishment of the design space for the method—"The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."[6] Traditional chromatographic method development has been dedicated to establishing a single set of chromatographic parameters that would result in an effective measurement. Within the scope of QbD, the design space can be a set of ranges for variables that have been proven to be effective. This concept becomes very useful when considering the robustness of a method (see below).

Critical Quality Attributes

Perhaps the greatest key to systematic method optimization is a clear definition of quality—the Critical Quality Attributes. Method development chromatographers will be familiar with critical quality attributes of methods, and indeed they will differ from project to project. Some examples of potential CQAs:

- Resolution of one or more components in the mixture from all other significant peaks
- Run time
- Detection limit
- Robustness

For practical purposes, detection limit is usually measured indirectly by examining peak width/tailing.

The objectives for a given final method should be fairly clear—for example, the method should be capable of resolving all peaks of interest in a reasonable time, retaining all peaks of interest, and should be robust. Most modern software systems are capable of optimizing multiple quality attributes for the chromatogram. The chromatographer should have the objectives clearly in mind before starting the method development process, and the tools will relate the chromatogram to a mathematical representation of the quality.

The most common approach to estimation of quality is to use a product or linearized product of the given quality attributes[7]. To effectively consider one quality attribute versus another, of course it is necessary to normalize the term, typically by assigning target values, with any value exceeding the target giving a suitability factor of 1, and values below the target as a ratio between 1 and 0. For the final stage of determining robustness the target range can be removed. Effectively the only allowed values for suitabilities are 0 and 1. Equation 1 and 2 describe a common approach to calculating individual suitabilities, and combination of multiple values into an overall suitability. The product approach to quality calculation enables software to sacrifice quality in one term to attain a large gain in another term, automatically. For example, the run time can be increased to a value somewhat higher than optimal in order to achieve better resolution.

$$S_i = 0 \quad \text{if } P_i \le P_i^- \qquad S_i = \left(\frac{P_i - P_i^{(-)}}{P_i^{(-)} - P_i^{(-)}}\right) \quad \text{if } P_i^- < P_i < P_i^+ \qquad S_i = 1 \quad \text{if } P_i \ge P_i^+ \tag{1}$$

Equation 1 describes the calculation of suitability of a given chromatogram CQA, where P_i^- is the lowest acceptable value for the CQA, P_i^+ is the value above which no additional benefit can be derived. S_i is the suitability for the parameter.

$$S = \sqrt[n]{(S_1 \times S_2 \ldots \times S_i)} \tag{2}$$

Equation 2 calculates the overall suitability of the chromatogram based on n different parameters.

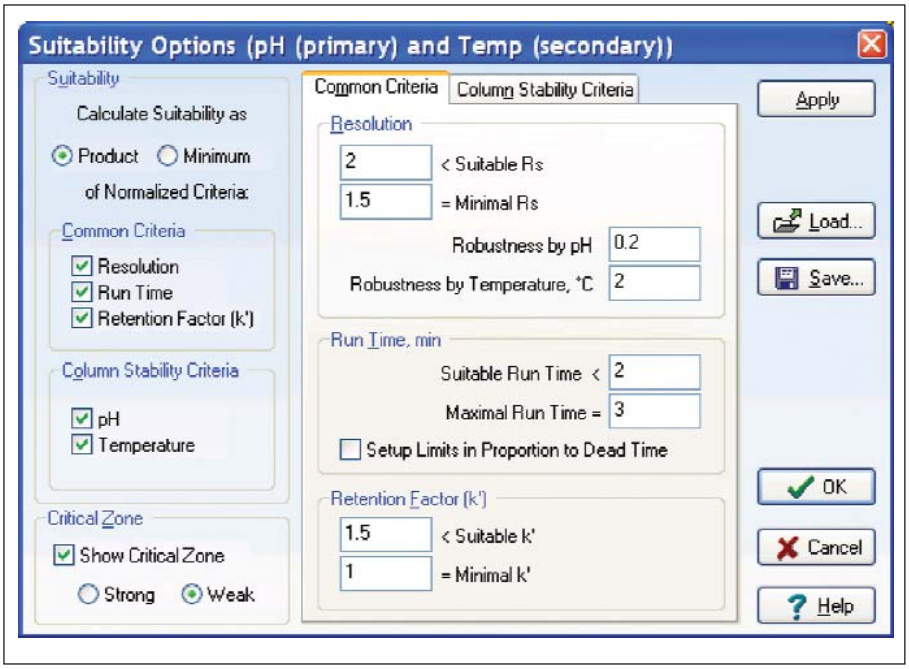

Figure 2. CQA definition dialogue in ACD/AutoChrom 12.02.

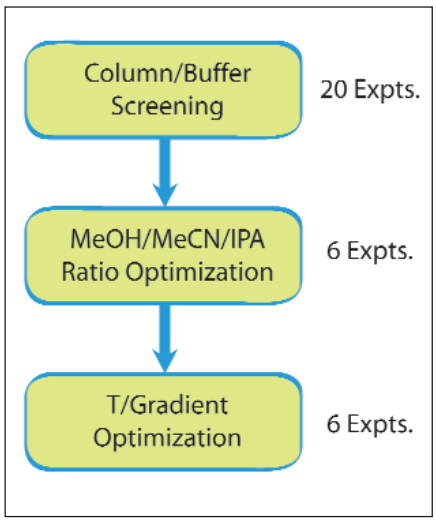

Figure 3. An example strategy for systematic method development.[8] 32 experiments enable the investigation of 6 variables.

Experimental Design

A clear aspect of QbD is the systematic, organised investigation of variables and their impact on quality. The variables to be investigated, and the interpretation approach can be considered to be the fundamental method development strategy. The strategy may have several steps, investigating variables in parallel or sequentially.

Multivariate Approaches

One aspect of QbD is the "dimensionality" of the strategy. Even with modern instrumentation and software, it requires an inordinate amount of time to investigate every potential parameter in parallel. Even if it were possible, this is dramatic overkill for most tasks at hand—we don't need to model gradient/temperature/pH for every candidate column, for example. Most modern approaches thus involve screening of certain parameters followed by optimization of others. Perhaps the most common is the parallel screening of column and buffer followed by optimization of temperature and gradient.

Screening vs. Optimization

Most modern method development strategies incorporate both screening and optimization. Screening is used for parameters that are typically viewed as discontinuous, such as column, buffer, and solvent choice. Optimization is reserved for parameters that are easy to treat as continuous, such as temperature and gradient design.

The screening of parameters illustrates a useful concept in systematic method development that should be kept in mind when establishing QbD methodology. While the CQA values are critical to the eventual optimization of the system, other decision-making tools may be necessary in the early stages of the work. Approaches as simple as counting peaks can be used for initial decision-making purposes, or more quantitative estimations of optimise-ability can be used to decide between potential values. In subsequent states, the definition of quality may be further and further refined.

The most commonly-applied tool for chromatographic method optimization is undoubtedly temperature/gradient optimization. A small number of experiments are collected varying one or both of these parameters, and used to create a global model of chromatographic response to any value of the variable. This approach has considerable utility in quickly locating an area of the overall experimental range that can give viable results, i.e., the location (but not definition) of a design space. Figure 5 shows a three dimensional representation of the suitability response surface for mobile phase composition and temperature.

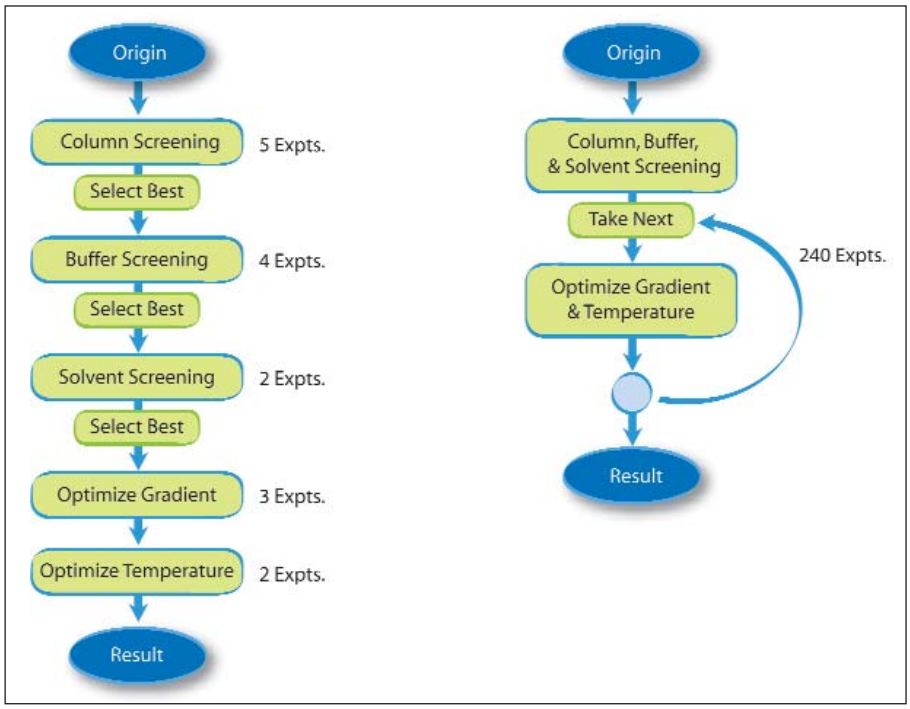

Figure 4. Univariate versus multivariate approaches to method development. In this example, sequential investigation of the parameters results in 16 experiments, versus 240 experiments for simultaneous investigation of all five parameters.

Data Collection and Extraction

Modern automated method development software greatly facilitates the collection of rigourous method development sequences by linking the experimental design tools to the injection sequence generation with appropriate equilibration routines. The largest traditional challenge in applying systematic method development concepts has typically been peak tracking. Global modeling tools generally require peak tracking in order to optimise systems. It is alternatively possible to directly model some quality attributes of methods using only a correct, unlabeled peak table. This can be a convenient approach for some systems, but accurate peak-picking is still a requirement. However, many key attributes of methods contain some elements of peak identity. For example, peaks associated with blanks, irrelevant impurities, excipients, and (for some applications) blocking compounds, such as phospholipids, typically need not be quantitated, but must be resolved from all relevant peaks to avoid impeding their effective measurement. In these cases, a simple approach of peak-picking is insufficient to measure quality attributes accurately, and peak tracking is a requirement.

Automated peak tracking has become more feasible in light of modern chemometric tools for tracking peaks based on LC/UV and LC/MS data.[10] Like peak picking, it is unusual to achieve 100% accurate, fully unattended peak tracking, and effectiveness can be a function of resolution of components. The sequential nature of virtually all method development approaches typically is compatible with this limitation; most approaches involve simple peak counting in screening experiments, followed by refinement of quality attributes in subsequent (optimization waves) to reflect resolution of specific components.

Measuring/Modeling Robustness

QbD is clear in that "quality" should be part of the design process. Virtually all CQA definitions will incorporate robustness into the

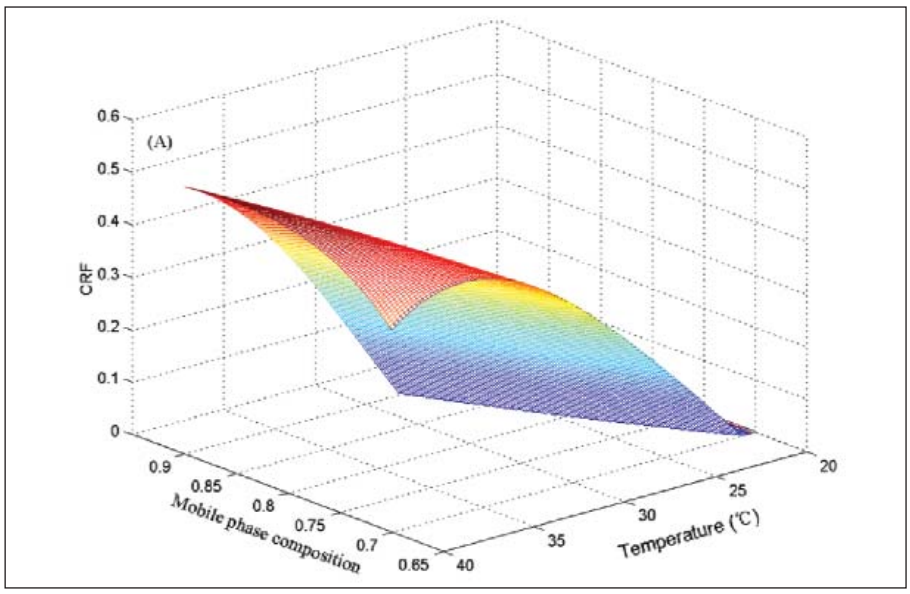

Figure 5. Parameter optimization. The quality of the separation in terms of critical pair resolution and run time is evaluated in terms of temperature and mobile phase methanol content.[9]

desired method qualities. Traditionally, after design is completed, robustness is measured, i.e., as part of the validation process. This approach is clearly in conflict with QbD principles—measuring robustness after design, rather than incorporating it with design. Indeed, most validation procedures incorporate an iterative approach in which the method is refined during the validation process. This can be very inefficient—a non-robust method may have to be abandoned or dramatically redesigned after validation has begun.

Temperature and solvent gradient can be optimised globally due to the well behaved response function of component retention time to variations of these parameters. Most other variables (e.g., pH and buffer concentration) cannot be optimised over a wide range without an inordinate number of experiments. However, these variables can obviously have tremendous influence on method quality; thus they can considerably impact robustness. It is therefore useful to limit the scope of the model to a reasonable range of values that is wide enough to permit useful optimization of robustness, but narrow enough to ensure accurate modeling.

All optimization tools incorporate the concept of optimization of quality into models. Visual examination of resolution maps can help to pinpoint areas of low/high robustness. Modern tools can even incorporate robustness into the optimization procedure, and reject areas of insufficient robustness automatically. Additionally, the same toolset can be used to measure robustness across an entire series of variables. Figure 6 illustrates this approach as an overlay on a standard resolution map—the range of viable values for the parameters is unshaded.

Robustness may be modeled for virtually any set of continuous parameters, but it is useful to note that many parameters are not as well-behaved as solvent and temperature, and so a relatively small range of training set parameter values should be used in order to ensure accuracy of the model. Robustness of the method will most often be modeled for parameters that are not globally optimised. This distinction is important, particularly for variables such as pH and buffer concentration, where it can be impractical to perform global optimization. Chromatographers may choose to perform multivariate optimization, or univariate optimization, depending on the time and instrumentation available, but additional rigour at this stage is consistent with Quality by Design philosophies, and should greatly facilitate validation.

"Edges of Failure"

The design space of the method is the range of investigated parameters that has been demonstrated to be viable and still obtain an effective method. This concept is closely related to robustness, but can also be used to establish the range of a given parameter in the design space. It is useful to note that there is no requirement in ICH guidelines to verify the edges of failure of the design space.

Control Strategy

A control strategy is designed to consistently ensure product quality. Chromatographers are very familiar with this concept. System suitability tests are a standard part of routine application of chromatographic methods today, and are typically established during method validation. Review of the characteristics of the chromatograms at the edges of failure of the design space should facilitate the definition of the control strategy, but this is likely to be a tentative recommendation that is confirmed in method validation.

Retention of Knowledge

During the course of chromatographic method development, a considerable amount of information about a given project is accumulated. In addition to accumulating spectral and method-specific retention information, we inherently learn chromatographic responses of given impurities to the various optimised variables. The robustness optimization stage of method development can indicate an effective design space (see above). Retention of this knowledge can facilitate post-validation

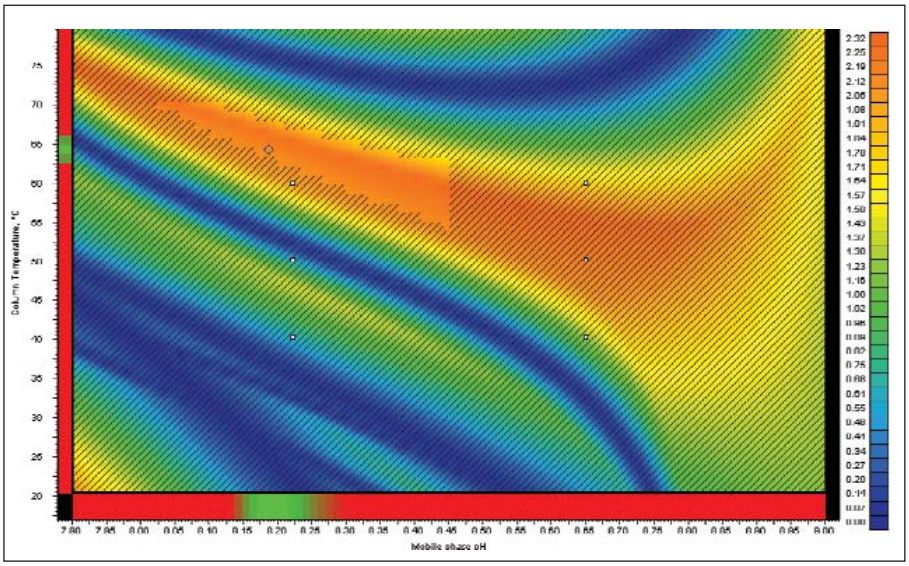

Figure 6. Modeling robustness of temperature and pH in AutoChrom MDS 12.02. The system models the movement of the peaks based on the range of parameter values. The unshaded region indicates the design space for these parameters.

adjustments of methods, within the existing design space, since working "…within the design space is not considered as a change."[6]. Retaining the design space information in terms of effective ranges of variables, can be valuable for post-validation adjustments, but even more efficient is the retention of the response surface for the system. In this context, adjustments to the method can be done quickly and efficiently based on the previously-determined model.

Conclusion

While Quality by Design is primarily a system for design of manufacturing processes to optimise product quality, most of the concepts can be effectively applied to optimization of chromatographic method quality, especially in light of modern hardware and software innovations. The QbD philosophy focuses decision-making systems on key measurable attributes of the method to ensure it is fit for purpose. The result is faster, more consistent chromatographic measurements.

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