

# Streamlined QbD HPLC Method Development with Automated Data Processing

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## Introduction

Quality by Design (QbD) has been widely applied to pharmaceutical manufacturing to enhance process robustness, and improve product quality and manufacturing productivity. Recently, there arose tremendous interests from both the pharmaceutical industry and regulatory agents to expand it to analytical methodology. Similar to process QbD, analytical QbD offers the benefits of more thorough understanding of both the measurement requirements and analytical methods,

thus delivers more robust methods. In addition, analytical QbD could significantly reduce the efforts relating to post approval variation. However, the approach would also mean significantly more experimentation to assess and understand the analytical method. This paper describes our attempts to apply some informatics tools to streamline the QbD method development to alleviate the increased resource burden.

## Quality by Design Principles<sup>1</sup>

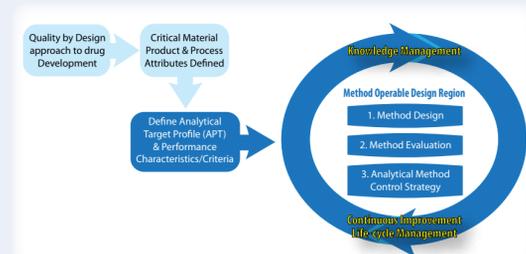


Figure 1. Components of application of quality by design (QbD) to analytical methods<sup>1</sup>.

**Analytical Target Profile (ATP)**—It defines what the method has to measure and to what level the measurement is required (i.e., performance level characteristics—such as precision, accuracy, working range, sensitivity—and the associated performance criteria).

**Critical Quality Attributes**—A quality attribute for which there is a substantial risk of impacting the safety or efficacy of a product.

**Method Design**—Systematic and science based method development to meet the ATP requirement.

**Method Evaluation**—Critical factors that may impact the method performance are evaluated with multivariate DOE or appropriate screening experiments.

**Control Strategy**—Define method parameter set points and operating space. Implement change control process.

**Knowledge Management**—All knowledge obtained from method design, evaluation and operating space definition should be retained and transferred with the method to allow future method life cycle management.

## QbD Method Development

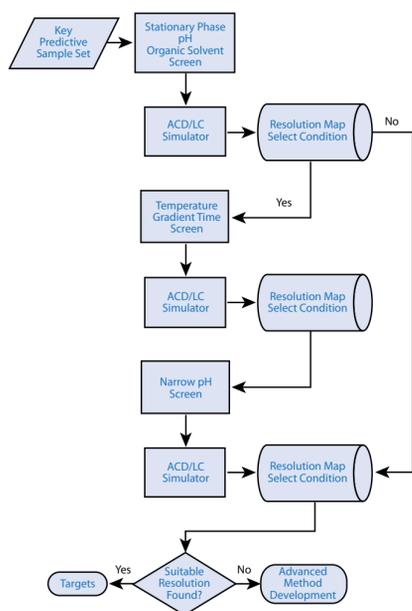


Figure 2. QbD RPLC Purity Method Development.

## ACD AutoChrom with Empower UPLC/SQD Control

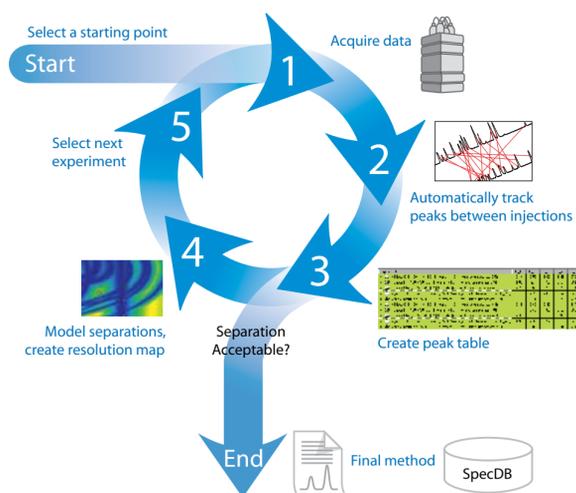


Figure 3. Automated execution of QbD RPLC method development with AutoChrom and Empower.

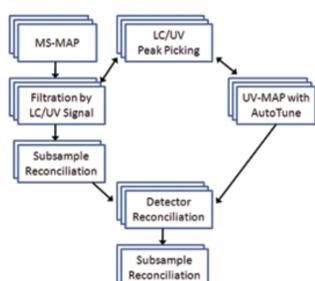


Figure 4. Schematics of automated data process (ADP) developed based on AutoChrom to integrate and track chromatography peaks for QbD experimentation reports.

## Experimental

**Automation Software:** ACD/AutoChrom MDS for Empower 2 v.12.02

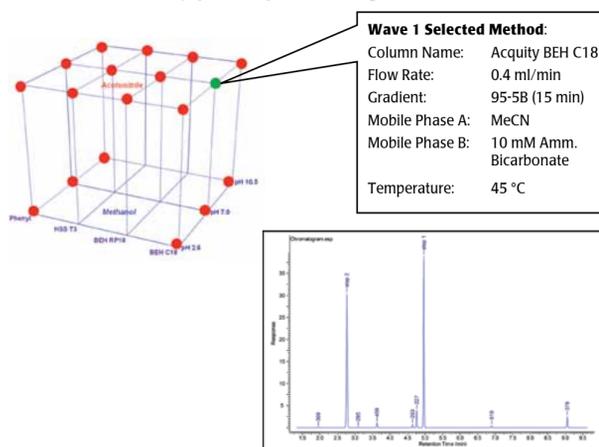
**Structure-based Modeling:** ACD/LogD Sol Suite v.12.02

**Chromatography Data System:** Waters Empower 2

**Instrumentation:** Waters Acquity with SQD MS detection

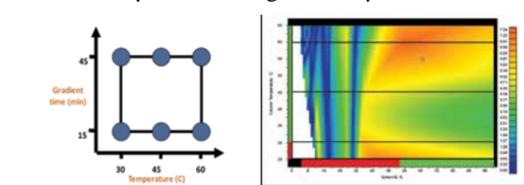
## Results

**Wave 1:** Stationary phase, pH, and organic modifier screen

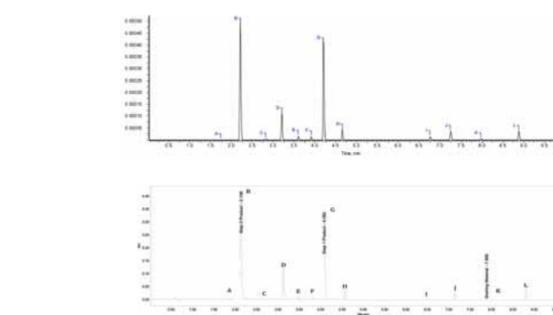


- Some impurities failed to retain at low pH and high pH respectively
- Neutral pH showed decent selectivity and good peak shape

**Wave 2:** Temperature and gradient optimization



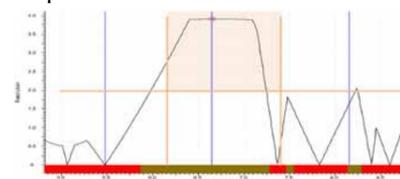
**Optimized Method:**  
BEH C18 2.1 x 100mm 1.7u, Temp=55C, Flow = .4ml/min, MP A = 10 mM Ammonium Acetate pH 6.65, MP B = MeCN, Gradient = 5% B to 65% B in 10 minutes



- All KPSS peaks shown. Excellent selectivity with short run time. Peak shape is excellent.

- Good correlation between simulated chromatogram and confirmation run

**Wave 3:** Narrow pH screen



**Final method:**

BEH C18 2.1 x 100mm 1.7u, Temp=60C, Flow = .4ml/min, MP A = 10 mM Ammonium Acetate pH 6.65, MP B = MeCN, Gradient = 5% B to 95% B in 15 minutes

## Discussions

- ACD/AutoChrom's direct control of the UPLC/SQD instrument makes the experiment setup rapid. The "intelligent" line purge and column equilibration automatically manages the required conditioning steps to help ensure data integrity.
- The Automated Data Processing (ADP) application contains all elements required to streamline the processing of the entire screening data set. Some processing parameters are being refined to minimize the required manual integration adjustment.
  - The data processing will automatically kick off once the screening completes.
  - Preset parameters will be used to integrate UV peaks and track with MS componentization.
- A comprehensive component table will be rendered with each chemical identity tracked across all screening methods.
- Pre-set parameters may not be ideal for all data sets, manual review and refinement is still required at the time of testing, which currently contributes to over 85% of the total analyst effort in the method development process.
- The total analyst time required for this development is 5 days.
- Following this development, risk assessment and corresponding robustness DOE was conducted to complete the definition of operating space, which is not covered here.
- Previously reported PACK application can upload all screen results to the project database for future knowledge transfer along with the final method.

## Conclusions

A QbD method development system has been designed that leverages structural knowledge of the samples in question, automation, chemometric data reduction, and software-based decision support. The result is a fast, efficient system that minimizes the amount of time that the chromatographer spends with the data, but investigates a very broad scope of experimental variables. Some refinement in the data processing parameters will take place in the future as well as interfacing with the DOE statistic package to provide a complete QbD workflow from samples to operating space.

## References

1. Mark Schweitzer, Matthias Pohl, Melissa Hanna-Brown, Phil Nethercote, Phil Borman, Gordon Hansen, Kevin Smith (Cephalon), Jaqueline Larew, "Implications and Opportunities of Applying QbD Principles to Analytical Measurements" *Pharmaceutical Technology*, Volume 34, Issue 2, 2010.
2. Mike McBrien, Gang Xue, Jeff Harwood, Yanqiao Xiang, Andrey Vazhentsev, "Building a Global Chromatography Knowledgebase for Method Development Prediction" HPLC 2009, Dresden, Germany, 2009.

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