INNOVATIVE HPLC METHOD DESIGN (DEVELOPMENT & UNDERSTANDING) WITHIN THE PHARMACEUTICAL LIFECYCLE

Dissertation

zur Erlangung des akademischen Grades des
Doktors der Naturwissenschaften (Dr. rer. nat.)

eingereicht im Fachbereich Biologie, Chemie, Pharmazie
der Freien Universität Berlin

vorgelegt von

Alexander H. Schmidt
aus Berlin
01. August 2017

Diese kumulative Dissertation ist im Zeitraum August 2012 bis August 2017 unter der Leitung von Frau Prof. Dr. Maria K. Parr angefertigt worden.

1.Gutachter:	Frau Prof. Dr. Maria K. Parr
2.Gutachter:	Herr Prof. Dr. Peter Surmann
Disputation am:	18. Dezember 2017

“Do it right the first time”

Imre Molnár

“Product features and failure rates are largely determined during planning for quality”

Joseph M. Juran

Danksagung

Ich danke Frau Prof. Dr. Maria K. Parr herzlich für ihre Bereitschaft, die Betreuung dieser Arbeit zu übernehmen. Außerdem möchte ich mich für die engagierte Unterstützung sowie für ihre weitreichenden wissenschaftlichen Anregungen sehr herzlich bedanken.

Bei Herrn Prof. Dr. Peter Surmann möchte ich mich herzlich für die Übernahme des Korreferats bedanken.

Mein ganz besonderer Dank gilt meinem Mentor Herrn Dr. Imre Molnár für die wissenschaftliche Förderung und Unterstützung über viele Jahre erfolgreicher Methodenentwicklungen und für die stets motivierenden und anregenden Diskussionen.

Meinem ehemaligen Mitarbeiter bei Steiner Arzneimittel und heutigen Geschäftspartner in unserer Firma Chromicent GmbH, Mijo Stanic, gilt mein Dank für die intensive Unterstützung bei der Durchführung der Versuche und der Umsetzung eigener Quality-by-Design Konzepte.

Abschließend möchte ich mich ganz herzlich bei meiner Familie bedanken, die mich in jeglicher Hinsicht unterstützt haben. Ihr Interesse an meiner Arbeit war mir ein stetiger Ansporn.

Inhaltsverzeichnis

1. Summary

High Performance Liquid Chromatography (HPLC) is an analytical separation technique and considered as the gold standard used in nearly all analytical laboratories in the pharmaceutical industry throughout the whole lifecycle of a drug product. As such HPLC is regulated with general chapters in all of the major pharmacopoeias (European Pharmacopeia, United States Pharmacopeia, etc.).

Despite the fact that the development of fast and reliable methods for drug analysis is of tremendous importance, up to now there is no regulatory guidance that addresses specific method development.
Therefore, method development has been performed in a traditional way by varying one factor at the time (OFAT), or by a more systematic approach, e.g. design-of-experiments (DoE), and software programs, e.g. modeling software, as an efficient and fast tool for method development.

In the first two studies presented in this thesis, modeling software is used to develop innovative and robust methods for complex (phytopharmaceutical) preparations. It allows for significant reduction of time for method development as only a minimized number of chromatographic runs need to be performed to develop resolution maps to identify the optimum chromatographic conditions. This is considered as most important aspect of this method development approach.

However, even the use of systematic method development strategies does not necessarily ensure the quality of the developed method in terms of robustness or transferability over the lifecycle of an analytical method. Furthermore, from a regulatory point of view, continuous improvement of the analytical method is difficult in the current system.

To improve robustness and reliability of pharmaceutical development the International Conference on Harmonization (ICH) Q8-guideline recommends a Quality-by-Design (QbD) approach based on sound science and quality risk management. The QbD concept may be extended to analytical methods and results in a systematic approach that includes definition of method goals, risk assessment, construction of a design

space, implementing a control strategy and continuous improvement to increase knowledge and ensure method robustness and transferability.

In a number of innovative and “ahead of the times” studies of pharmaceutical interest, systematic method development strategies in a Quality-by-Design framework are presented. The benefits of applying Quality-by-Design principles are discussed. Sources of variability are identified and minimized as well as intended performance requirements are ensured using these methods -. Due to the knowledge gained within the development stage the resulting very robust analytical methods will have fewer issues and failures rates throughout their lifecycle. Furthermore, working within the design space of a method can be seen as an adjustment and not as a post approval change. The novelty and opportunity in this approach are discussed in detail..

2. Zusammenfassung

Die Hochleistungs-Flüssigchromatographie (HPLC) ist eine analytische Trenntechnik und gilt als Goldstandard, die in fast allen analytischen Laboratorien in der pharmazeutischen Industrie während des gesamten Lebenszyklus eines Arzneimittels verwendet wird. Als solches werden Regeln zum Einsatz von HPLC in allgemeinen Kapiteln in allen großen Pharmakopöen (Europäische Pharmakopöe, United States Pharmacopeia, etc.) aufgestellt.

Trotz der Tatsache, dass die Entwicklung von schnellen und zuverlässigen Methoden für die Arzneimittelanalyse von enormer Bedeutung ist, gibt es bislang keine regulatorische Richtlinie, die eine spezifische Methodenentwicklung thematisiert.
Daher wird die Methodenentwicklung häufig auf herkömmliche Weise durchgeführt, z.B. durch aufeinander folgende Variation von Faktoren (one factor at the time, OFAT) oder durch einen systematischeren Ansatz unter Verwendung von Techniken, z.B. Versuchsplänen (Design-of-Experiments, DoE) und Software-Programmen, z.B. Modellierungssoftware, als effizientes und schnelles Werkzeug für die Methodenentwicklung.

In den ersten beiden Studien, die in diese Arbeit eingeflossen sind, wird eine Modellierungssoftware verwendet, um innovative und robuste Methoden für komplexe (phytopharmazeutische) Arzneimittel zu entwickeln. Die Zeit, die für die Durchführung der notwendigen Anzahl von chromatographischen Läufen zur Entwicklung von Auflösungskarten zur Ermittlung der optimalen chromatographischen Bedingungen eingespart wird, ist der wichtigste Aspekt des Methodenentwicklungsansatzes.

Doch auch der Einsatz systematischer Methodenentwicklungsstrategien gewährleistet nicht zwangsläufig die Qualität der entwickelten Methode hinsichtlich Robustheit oder Übertragbarkeit über den Lebenszyklus einer analytischen Methode. Ferner ist aus regulatorischer Sicht eine kontinuierliche Verbesserung der analytischen Methode im gegenwärtigen System schwierig.

Zur Verbesserung der Robustheit und Zuverlässigkeit der pharmazeutischen Entwicklung empfiehlt die Q8-Leitlinie der Internationalen Konferenz zur Harmonisierung (ICH) einen Quality-by-Design (QbD) Ansatz, der auf fundierte wissenschaftliche Kennnisse und Qualitätsrisikomanagement basiert. Das QbD-Konzept kann auf analytische Methoden erweitert werden und führt zu einem systematischen Ansatz, der die Festlegung von Methodenzielen, die Risikobewertung, die Konstruktion eines robusten Bereiches (Design Space), die Anwendung einer Kontrollstrategie und die kontinuierliche Verbesserung zur Steigerung des Wissens wie auch die Sicherstellung der Methodenrobustheit und Übertragbarkeit beinhaltet.

In einer Reihe innovativer und vorausschauender Studien von pharmazeutischem Interesse werden systematische Methodenentwicklungsstrategien in einem Quality-by-Design Rahmen vorgestellt. Die Vorteile der Anwendung von Quality-by-Design-Prinzipien, die Ermittlung und Minimierung von Variationsquellen und die Sicherstellung, dass die Methoden den beabsichtigten Leistungsanforderungen entsprechen, werden diskutiert. Die daraus resultierenden sehr robusten analytischen Methoden werden aufgrund der in der Entwicklungsphase gewonnenen Erkenntnisse weniger Probleme und Ausfallraten während des gesamten Lebenszyklus aufweisen. Damit kann das Arbeiten innerhalb des robusten Bereichs einer Methode als Anpassung und nicht als Änderung nach der Zulassung gesehen werden. Die Neuheit und Chance in diesem Ansatz werden im Detail diskutiert.

3. Introduction

High performance liquid chromatography (HPLC) is a widely used separation technique across numerous industrial fields including sectors such as pharmaceuticals, agriculture, consumer products, and environmental testing [1].
Its present popularity is attributed to its convenient separation used for the analysis of almost any sample that can be dissolved. Separation of compounds is achieved upon differences in the distribution of analytes between the stationary and the mobile phase. Detailed information on this technique and examples of its application can be reviewed in popular reference publications [1-5].

In the pharmaceutical industry HPLC is considered as the gold standard used throughout the whole lifecycle of a drug product, from discovery of the drug substance, development of the drug formulation, through clinical testing for regulatory approval and quality control of manufacturing of the final drug product. For example, individual HPLC methods are used ….[1, 6]:

- to evaluate the optimum formulation (including container/closure system)
- to evaluate setting of specifications for drug substances, intermediates and drug product
- to evaluate the shelf-life of the product (stability)
- for identification and quantification of active pharmaceutical ingredients (APIs), their impurities and degradants
- to support process development and validation study (incl. cleaning validation)
- to support preclinical and clinical studies (product safety and efficacy)

The majority of HPLC separations of small molecules (neutral, weak acid and weak base below 1,000 Daltons) are performed on reversed phase columns [7]. Only small portions of samples require special columns. Examples include carbohydrates on amino-bonded phases, very hydrophobic compounds on normal-phase or HILIC stationary phases, strong acids or bases on ion exchange columns or chiral compounds on chiral HPLC phases [4, 7].
HPLC is also widely used when analyzing large biomolecules in the size exclusion and ion exchange mode as well as HILIC and reversed-phase mode.

The main benefit of (reversed phase) HPLC is its selectivity: Hydrophobic (non-polar), hydrophilic (polar), ionisable and ionic compounds can all be separated, under certain conditions but rarely simultaneously. The reason behind this almost universal applicability are the many factors that can be adjusted in order to affect how a particular analyte will interact with both the stationary and the mobile phase [8].

While HPLC is a very established reliable technique and is adequate in controlling pharmaceutical purity and consistency, it still could be improved. For example, a drug product may have several impurities of synthesis intermediates and/or degradation impurities, at 0.1 % levels relative to the drug substance with a wide range of polarities. Because of the complexity of these samples, gradient elution is required with separation times of usually 30 min and more. Reducing the separation time, without losing the quality of the separation requires generating higher resolution power [1, 9].

The resolution of neighboring peaks can be expressed by the general equation (figure 1) for resolution comprised of physical and chemical parameters that effect chromatographic resolution: efficiency (N), selectivity (α) and the retention factor (k).

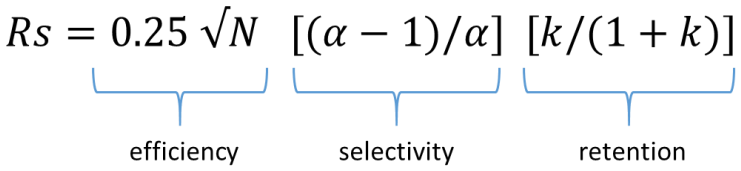

Fig. 1: General equation for resolution. (N) is efficiency, expressed by the plate count, (α) is selectivity and (k) is retention factor.

Selectivity (α) and the retention factor (k) are chemical parameters that can be affected by modifications of the mobile phase composition, column chemistry and temperature [4]. Efficiency (N) is a physical parameter that is more difficult to manipulate but have a significant impact on resolution. Small particle sizes of the stationary phase result in narrower peaks, and thereby in higher efficiencies of the columns [10].

The increased resolution by smaller particle size of the column packing is the factor responsible for the development of the so called ultra high performance liquid chromatography (UHPLC) technology. The principles of this evolution are illustrated

by the van Deemter equation (figure 2) as the relationship between linear velocity and plate height.

$$\mathrm{HETP} = \underbrace{a(d_p)}_{\text{A term}} + \underbrace{b/u}_{\text{B term}} + \underbrace{c(d_p)^2\, u}_{\text{C term}}$$

Fig. 2: van Deemter equation. (HETP) is height equivalent to a theoretical plate, (a), (b) and (c) are diffusion related terms, (d_p) is the particle size and (u) is the linear velocity.

According to the van Deemter equation, decrease in particle size increases the efficiency of separation [1, 9, 10], as can be seen in the figure 3.

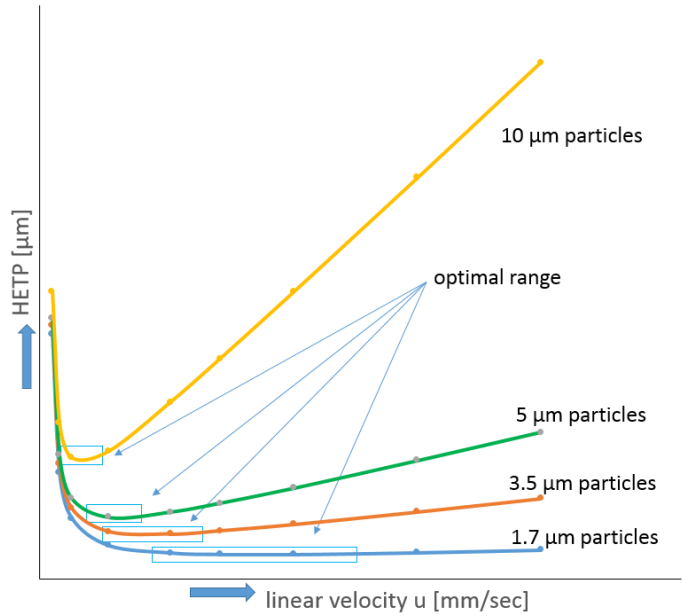

Fig. 3: Simulated van Deemter plot comparing different particle sizes

Control over each of those factors through particle size and chromatographic conditions allows the development of fast and reliable methods for pharmaceutical analysis.

4. Aim of the Work

Development of fast and reliable methods for pharmaceutical analysis is only the first step in the integrated approach of the analytical method lifecycle, which refers to the combined activities of analytical method development, robustness testing, method validation and transfer, and continued improvements to ensure that the method is best suited for their intended use.

Despite the fact that the development of fast and reliable methods for pharmaceutical analysis is of tremendous importance to the pharmaceutical industry, up to now there is no regulatory guidance available that address specific method development.

Aim of this work is to apply modern strategies to the development of analytical methods for a couple of analytes of pharmaceutical interests. The strategies included computer-assisted chromatographic modeling and design-of-experiments in a quality-by-design framework as well as *in-silico* robustness testing of already existing methods.

5. Background on HPLC Method Development*

5.1. Basic Instrumentation for HPLC Method Development

There are several basic components of a HPLC system used to facilitate method development [11]. HPLC systems can be modular or integrated, and utilize either isocratic or gradient solvent delivery. As method and column screening is a method development approach commonly used to investigate potential starting conditions for further method optimization, a typical “workhorse system” for method development consists of the following:

- a gradient solvent delivery manager (gradient pumps) with solvent switching valve to deliver up to 9 different eluents (usually 3 organic solvents and 6 buffers with different pH values)
- an automatic sample manager with temperature controlled sample compartment
- a column oven with switching valve for up to 4 columns at two different temperature zones
- multiple detector capabilities including photo-diode array and mass spectrometry.

Fig. 4: Example of modular LC system in typical method development configuration

* Parts of this chapter were published as a review of life cycle management of analytical methods [141].

This system, as displayed in figure 4 is capable of delivering mobiles phases consisting of different blends, pHs and four or more columns operated at different temperatures [12].

Equivalent and/or orthogonal columns with respect to any selected column can be evaluated [7, 13-16] by using the Hydrophobic Subtraction Model (proposed by Snyder, Dolan and Carr and known as the PQRI approach).

The model was developed on the basis on retention data for a series of standard mixtures and the same separation conditions and show that five column properties completely account for column selectivity. Therefore, every reversed-phase column can be characterized and their similarity (or orthogonality) can be indicated by a selectivity factor F_s.

Over 650 columns have been tested, characterized and added to the database [8, 17]. This database is available on the USP website [http://www.usp.org/pqri-approach-column-equiv-tool, accessed 15.04.2017].

In general, most of the basic HPLC systems have remained unchanged for at least 30 years but in 2004 one of the first true advantages was introduced by Waters with an UHPLC system capable of operating up to 15,000 psi (1,000 bar), which allow the use of columns packed with sub-2 µm particles [10, 18-24].

Currently, the innovative UHPLC technology is the standard equipment for the method development laboratory, driven by the ever-expanding need and challenge to get more and better information faster, all in an economic climate where cost control is a primary concern [25-27].

5.2. Traditional Method Development Approach

Strategic method development depends on the knowledge and complexity of the sample, the analyst's experience, and intuition, availability of materials such as columns and solvents, as well as the goals of the separation.

In the past, choosing conditions for a final separation (method development) was often carried out by a trial-and-error approach [26], for example by varying one-factor-at-a-time (OFAT) and examine the resolution of peaks until a suitable method was found. This approach was not only time-consuming and often resulted in a non-robust performance (new peaks, disappearance of other peaks and changes in critical peak

pairs), especially when transferred into another lab because interactions between chromatographic parameters (factors) were not considered [28-31].
Hence, the traditional method development strategy has a high risk in method failure (e.g. non-confirmed out-of-specification result) and always requires an extensive revalidation protocol after method transfer or alternative method development. Thereby it may result in increasing costs of the method [32].
Thus, there is a tremendous desire to develop a chromatographic method in a more systematic approach of screening columns and mobile phase buffers to gain knowledge about the influential parameters and to set the optimized conditions for the separation.

A similar effort as for the development of a chromatographic method should be spend on the development of the sample preparation procedure. Physico-chemical properties of analytes and matrices, as solubility, reactivity and stability, should be considered.
Suitable sample preparation protocols for complex samples are crucial to every HPLC method development project. When too little effort is spend, the following may often be observed [33-37]:

- Method robustness problems
- Method transfer problems
- Poor or irreproducible recovery
- Short HPLC column lifetime
- High pressure or blocked columns

Accurate sample preparation for HPLC analysis intends that samples are reduced in matrix components and are free from particles, while the analytes (e.g. drug substance and any possible impurity or degradant) are extracted with optimal recovery. Typical clean-up methods include liquid-liquid extraction, soxhlet extraction, solid phase extraction, filtration and centrifugation. A summary of different sample preparation techniques for pharmaceutical products can be found in the literature [22, 33-36].

5.3. Systematic Method Development Approach and Quality-by-Design

A more systematic approach uses techniques and software programs as an efficient and fast tool for method development can be grouped into two categories:

The first group includes chemometric techniques [38-42]. In a full or fractional factorial design a set of experiments (Design-of-Experiments, DoE) is carried out in which one or more factors are changed at the same time. Using statistic tools the effect of each factor on the separation can be calculated and the data be used to find the optimum condition of a separation. Typical examples are the widespread use of the Plackett-Burman design [41-44]. It requires 4n experiments to be performed to investigate a maximum of 4n-1 factors at two levels [38].
Two level designs can only lead to linear models of response and therefore can not give information about non-linear relationships. However, a drawback of full-factorial design at levels higher than two, is the increased number of experiments to be performed [38]. As alternative designs that allow higher number of levels without performing experiments at every combination of factor levels as the central composite design and Box-Behnken design may be applied for method development [38, 45, 46].

In an effort to minimize the number of experiments needed for analytical method development other widespread strategies are using the molecular structure, or physicochemical properties such as logP, logD and pKa of the sample components to estimate their retention and optimal separation conditions [4, 47-49]. For example, column selection and best pH working range can be deduced from logD-pH-diagrams if the structure of all compounds (e.g. API and known impurities) are known and logD values can be calculated (either by software programs and databases) [66].
With the emerging interest in large molecule based drug products structure related retention time prediction gains even more interest. These model-based approaches are referred to as quantitative structure activity (QSAR), property (QSPR) or retention relationships (QSRR) and proved a scientific rationale for the use of stationary and mobile phase combinations [50-55]. Some software packages (e.g. Chromsword, ACD/ChromGenius) uses prediction of retention based on the molecular structure of the compound itself.

The second group includes computer-assisted modeling packages (e.g. DryLab) that use measured retention data to predict chromatograms at selected conditions [7, 9, 11, 56-58]. Based on a small number of experiments these software applications can predict the movement of peaks in reversed-phase and other liquid chromatography

separations when changing the mobile phase composition, pH, temperature, flow rate, gradient ranges and steps, or column dimensions and particle size [30, 59-67].

In the last couple of years lots of manuscripts have been published on systematic method development strategies using software programs [4, 5, 56-58, 68-69].
Examples from own investigations are given in manuscript 1 and 2 [70, 71].

Indeed, even the use of systematic development strategies do not ensure necessarily the quality of the developed method in terms of robustness or method transferability [72-73].

A systematic approach is also recommended by the US Food and Drug Administration's (FDA's) "*Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century – a risk based approach*" initiative [74]. It was promoted after FDA identified that pharmaceutical manufacturing problems are not fully understood and that the implementation of new state-of-the-art technologies was slower than in other industries [75-77]. The initiative resulted in the development of a series of new guidelines issued by the International Conference on Harmonization (ICH):
The ICH guidelines Q8 [78] and Q9 [79], issued in 2005, to provide guidance in pharmaceutical development and risk management, while the 2008 issued Q10 guideline [80] describes a holistic and integrated pharmaceutical quality system. In 2012 the Q11 guideline [81] on development and manufacture of drug substances was added.
These guidelines were intended to modernize the pharmaceutical industry's approach for development and manufacturing of pharmaceuticals to a more scientific and risk-based approach [77].
Although the ICH guideline Q8 does not explicitly mention analytical method development, a Quality-by-Design (QbD) approach in pharmaceutical development is requested. Quality-by-Design, as defined by the revised ICH guideline Q8(R2) [78], is "*a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management*".

Quality-by-Design is a concept first outlined by Joseph Juran, a well-known expert and consultant in quality, who stated that *"product features and failure rates are largely determined in planning for quality"* [82]. This means that quality must be designed into a product or a process and cannot be tested into it.

The QbD concept can be extended to analytical methods and results in a systematic approach that includes definition of method goals, risk assessment, building of a design space, implementing a control strategy and continual improvement to increase method robustness and knowledge. To distinguish this from the Quality-by-Design concept for processes, it is often called Analytical Quality-by-Design (AQbD) in recent publications [32, 83-87], see figure 5.

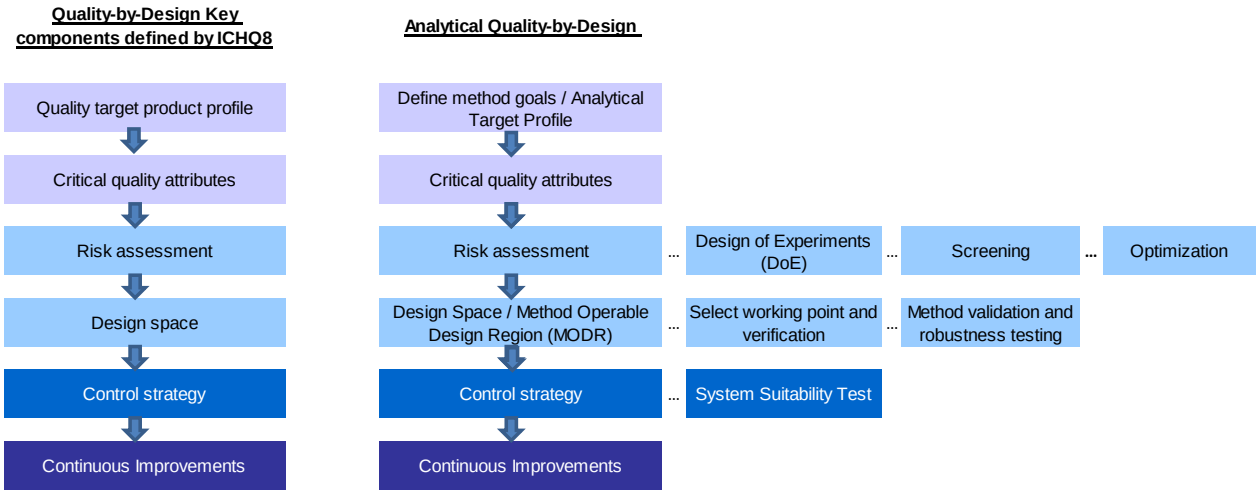

Fig. 5: Comparison of the Quality-by-Design key components defined by ICH Q8 and Analytical Quality-by-Design (AQbD) [141]

The use of design of experiments (DoE) methods are extensively applied in method development to understand the effects of possible multidimensional combinations and interactions of various parameters. Application of a DoE strategy provides scientific understanding and leads to establishment of a "design space" [88]. Therefore, the use of DoE in AQbD strategies may replace the one-factor-at-the-time (OFAT) approach in method development, in which one factor after another is optimized.

AQbD includes an early risk assessment to clearly identify method parameters that have an impact on the performance of the analytical method but also risks associated

with variability such as sample preparation, instrument configuration, and environmental conditions [32].

The quality risk management (QRM) process is described in detail in ICH Q9 guideline [79] and comprised of risk assessment, risk control, and risk review.

Risk assessment using “Fishbone” (Ishikawa) diagram or failure mode effect analysis (FMEA) and prioritization matrix (PM) may be employed throughout various stages in the development of an analytical method to assess method factors with the highest effect on method performance and define which (if any) require additional investigation [89-92]. A simplified example of a “Fishbone” (Ishikawa) diagram for a purity LC method is shown in figure 6.

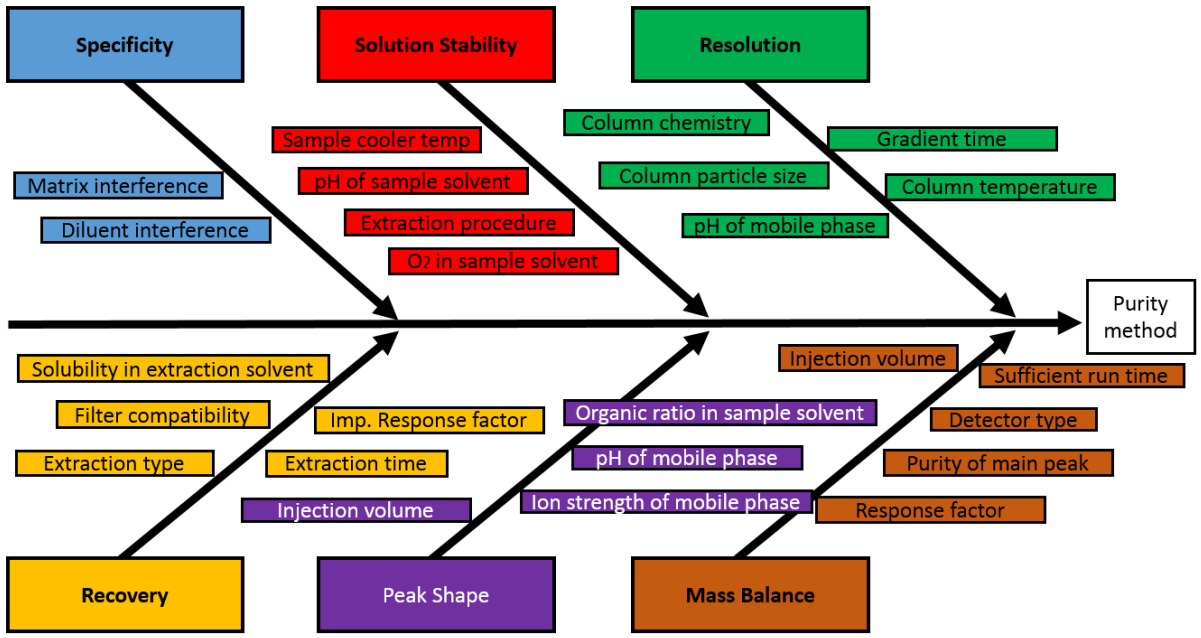

Fig. 6: Ishikawa diagram for risk assessment of a liquid chromatographic purity method

Once the fishbone diagram is constructed, selected method parameters are subject to a risk assessment. By using DoE (e.g. full or fractional factorial designs, Plackett-Burman design) the most critical method parameters (influencing factors) are optimized simultaneously to assess the effect of the critical parameters individually and in combination.

An example of a DoE for three (p) method parameters at two (n) levels each is given in figure 7 and leads to 8 ($E=n^p$) experimental runs. [7].

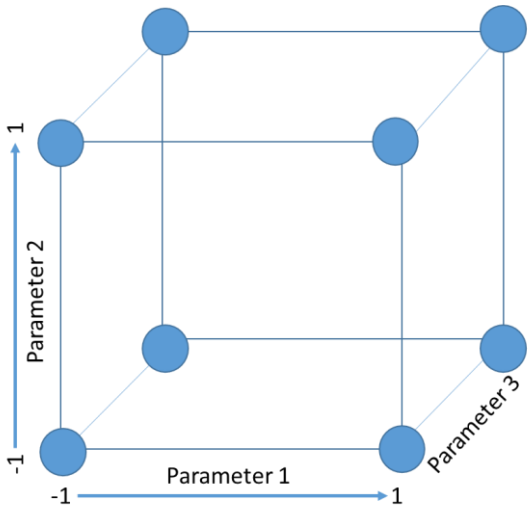

Fig. 7: Overview of a full-factorial screening design, with the parameters 1, 2 and 3 as variables. Each variable is changed at two levels making eight possible combinations (experimental conditions).

The output of the DoE leads to the identification of a region of robust operating conditions, the so called Design Space (DS) [59, 64, 66, 78, 93, 95] or Method Operable Design Region (MODR) [32, 84, 91, 96, 97]. More details can be found in the literature [32, 59, 64, 66, 78, 84, 90, 91, 98].

Afterwards a working point within the Design Space (or MODR) is chosen and method verification is performed to confirm the ability of the method to meet the requirements of the previously defined method goals (Analytical Target Profile, ATP). Further method validation in compliance to applicable regulations [99] is mandatory.
The verification and validation experiments may demonstrate the robustness of the method across the parameter range from low to high through a target value of a variable [32].

Once method development and validation is completed, a method control strategy is established based on the risk assessment and data available. The method is then implemented for routine use where continuous monitoring of the method performance over the time is established (e.g. by using control charts) and improvements - when needed - take place [32, 92].

The novelty and opportunity in this approach is that modifications within the Design Space (Method Operable Design Region) of a specific method may be seen as an adjustment and not a (post approval) change [30, 89].

Using the QbD approach the fundamentals of a systematic method development have not changed. However, there is an increased demand to design adequate quality into the method, e.g. by DoE strategies. The introduction of an early risk-assessment helps to identify critical analytical parameters and to concentrate on them in method development [30, 100]. A deeper understanding of what we are doing and why we are doing it in the laboratory is required. The idea is to invest more time, consideration and good scientific know-how into the early stages of a separation in order to prevent problems later on (e.g. frequently non-confirmed out-of-specification results due to the non-robustness of the method) [7, 101, 102].

5.4. Lifecycle of the Analytical Method

In recent publications in the USP Pharmacopoeial Forum [103, 104] the USP Validation and Verification expert panel discussed how modern concepts of a lifecycle model may be applied to analytical methods and proposed a new General Chapter <1220> *"The Analytical Procedure Lifecycle".* The concept is based on process validation (FDA Guidance for Industry: Process Validation [105]) and also described in ICH guidelines Q8, Q9, and Q10 [78-80].

The lifecycle concept applies the Quality-by-Design approach to method development, validation and operational use and would be a link between method development and method validation within a Pharmacopoeia [101, 102].

Up to now, four stimuli articles regarding the analytical lifecycle have been published:

- "Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification" [103]
- "Fitness for Use: Decision Rules and Target Measurement Uncertainty" [106]
- "Analytical Target Profile: Structure and Application Throughout The Analytical Lifecycle" [107]
- "Analytical Control Strategy" [108]

5.4.1. Analytical Target Profile

As stated in the stimuli article [104] "*A fundamental component of the lifecycle approach to analytical procedures is having a predefined objective stipulates the performance requirement for the analytical procedure. These requirements are described in the ATP"* (Analytical Target Profile).

The ATP may be seen as a reference point of the lifecycle approach of an analytical method. It is comparable to the Quality Target Product Profile (QTPP), which is defined in ICH Q8 [78] for analytical method development. The ATP is a predefined written record of the performance requirements of an analytical method. It should be established prior to method development and linked to the purpose, not to a specific analytical technique. That means that any analytical procedure that conforms to the ATP is acceptable [109].

The ATP criteria should be based on the intended use of the analytical method. Customer specifications or regulatory requirements and guidelines may be used as basis for the ATP. In case of quantitative methods the ATP is very often based on the target measurement uncertainty (TMU), which is the maximum acceptable uncertainty in the reportable result that must be achieved by the method in order to make decisions with confidence [106, 110].
Therefore, key to the assessment of compliance is the concept of "decision rules". These rules give a prescription for the acceptance or rejection of a product based on the measured quantity value, its uncertainty and the specification limit or limits, taking into account the acceptable level of the probability of making a wrong decision [106, 110]. The concept of decision rules is also described in consensus standard documents such as the "Guideline for Decision Rules" of the American Society of Mechanical Engineers (ASME) [111], the Eurachem Guide "Use of uncertainty information in compliance assessment" [112], and "Guide to the Expression of Uncertainty in Measurement (GUM)" of the International Organization for Standardization (ISO) [113].

Depending on the intended use of the method, typical performance criteria are:

- Accuracy
- Precision
- Selectivity
- Sensitivity
- Linearity
- Robustness,

but also

- speed and throughput capacity
- costs
- ease of operation.

The ATP defines how accurate and precise the method should be. An example of an ATP for an impurity method of a drug product may be that *"…the procedure must be able to accurately quantify the drug substance in the presence of impurities and excipients with the requirement for accuracy of 100.0 % ± 3.0 % and precision of ≤ 1.0 %..."* [107].

Once the ATP has been defined and an analytical technique that is cable of delivering analytical data/results compliant to the ATP selected, a method can be designed and a risk assessment should be undertaken.

Application of lifecycle management concepts to analytical procedures provides an opportunity to use the knowledge gained from the application of scientific knowledge and quality risk management to continuous improvement and assurance of data quality. Analytical method lifecycle management combines activities of analytical method development, improvement, qualification, validation, transfer and maintenance related to GMP production [114].

The lifecycle approach for an analytical procedure is outlined in figure 8 and is an extension of the current guidelines, taking advantage of the Quality-by-Design approach [107].

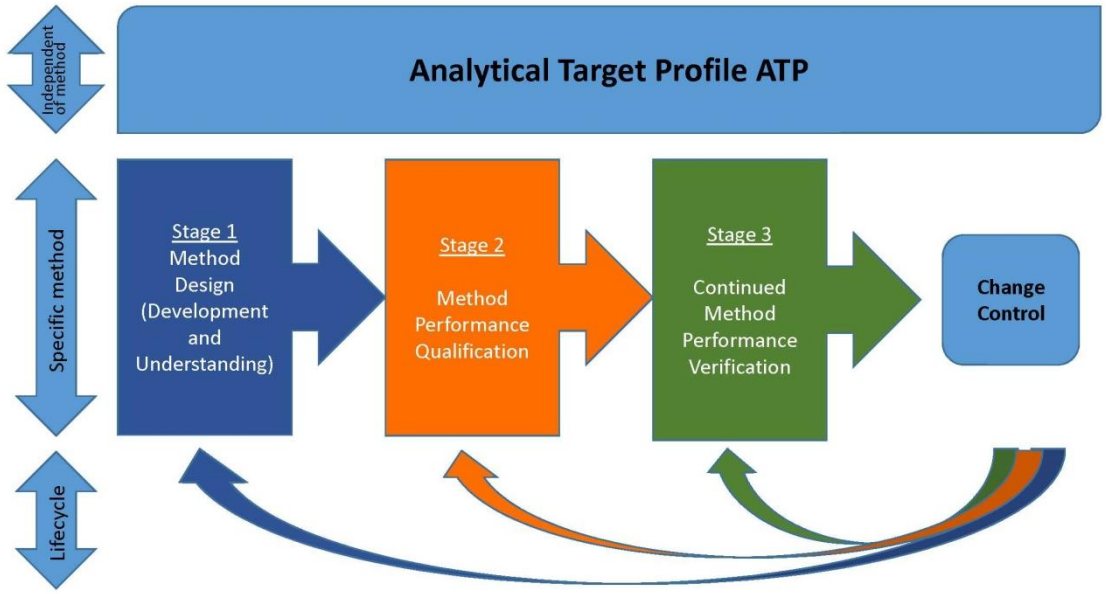

Fig. 8: Life cycle management in analytical methods [141]

5.4.2. Stage 1 – Method Design (Development and Understanding)

The first step of the process is method design (method selection, development and understanding). It is important to understand the method fundamentals by knowing the key variables and how these may influence the analysis [101]. Identification and investigation of potential analytical variables can be performed using risk assessment and robustness studies. The knowledge should be used to establish a design space (MODR) and build the foundation of an analytical control strategy. It is important to consider all aspects in the development stage, including sample preparation as well as preparation of reference solutions [33] to ensure that the final method is robust. Application of Quality-by-Design principles in method development as described in the previous section is mandatory.

Once the design, development and understanding stage of the proposed procedure has been finished and the knowledge well documented (“Knowlegde Management Report”), the method is ready to be qualified in stage 2 of the lifecycle.

5.4.3. Stage 2 – Method Performance Qualification

The second stage is the method performance qualification, which is actually traditional method validation - found in the ICH guideline Q2 “Validation of Analytical Procedures: Text and Methodology” [99] - under another name, adapted from the FDA Guidance for Industry on Process Validation [105]. This guidance was revised in 2011 to better align with the US Food and Drug Administration’s “*Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century – a risk based approach*” initiative [74] and the ICH Q8, 9 and 10 [78, 79, 80] and comprised a product lifecycle concept.

As mentioned before, not only the process validation can benefit from the product lifecycle but also method validation [115-120]. Therefore method validation may be defined as “*The collection and evaluation of data and knowledge from the method design stage throughout its lifecycle of use which established scientific evidence that a method is capable of consistently delivering quality data*” [89, 115, 116].

Build on the results of stage 1, the purpose of the performance qualification is to confirm that the method will operate (in routine use) as intended and meets the previously defined ATP criteria. It should be performed in the laboratory, which will be using the procedure routinely and in this case it may replace the current method transfer approach, which includes comparative testing, method co-validation, method revalidation or a transfer waiver as alternative strategies [121, 122] as requested by USP General Chapter <1224> *Transfer of Analytical Procedures* [123] and <1225> *Validation of Compendial Procedures* [124].

5.4.4. Stage 3 – Method Performance Verification

An important aspect in the lifecycle approach is Stage 3, the Method Performance Verification that checks how the method operates in routine use and that the resulting data are fit for the intended use (meaning accurate and precise).
A statement how “*verifying an acceptable level of performance of an analytical system in routine or continuous use”* [125] can be found in USP General Chapter <1010> *Analytical data – Interpretation and Treatment*. It includes an ongoing program for

routine monitoring of analytical performance data and can be achieved through… [108, 125]

- tracking of real samples (e.g. from batch release) or standard results (trend analysis charts)
- trending of system suitability data
- assessing precision from stability studies [126]
- analysis of a reference batch.

If data indicate that the method is not operating as expected (e.g. causing lab related out-of-specification results), it should be investigated to identify the root cause of the variation. The outcome of this investigation may be a change to the method and the nature of the change dictates the action that should be taken: it may be a change to the method design (stage 1) and/or causes re-qualification (stage 2).

5.5. Fitness for purpose concept

According to EURACHEM guide to method validation and related topics "a*nalytical measurements should be made using methods and equipment which have been tested to ensure they are fit for purpose*" [127].

To evaluate the fitness for purpose of an analytical method data gained during method performance qualification and verification need to be judged in the light of the preset ATP.

In addition, qualification of instruments and systems can positively or negatively influence the analytical lifecycle. If an analytical system is not installed correctly, the environment is not suitable for the instrument or the instrument is not operated correctly the analytical data/results are not valid.

According to USP General Chapter <1058> *Analytical Instrument Qualification* [128] can be seen as the base for reliable and consistent data (data quality). Therefore, a qualification process based on the "4Q model" is typically used to demonstrate that an analytical system is fit for purpose [128, 129].

The 4Q model qualification process consists of the four phases:

- Design Qualification (DQ)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

The USP chapter <1058> provides definitions for each of the four phases [128].

As illustrated in figure 9, the qualification process starts with the Design Qualification (DQ), in which the user defines his requirements for the instrument and the analytical method (User Requirement Specification, URS), compares them with the specification of the instrument manufacturer.

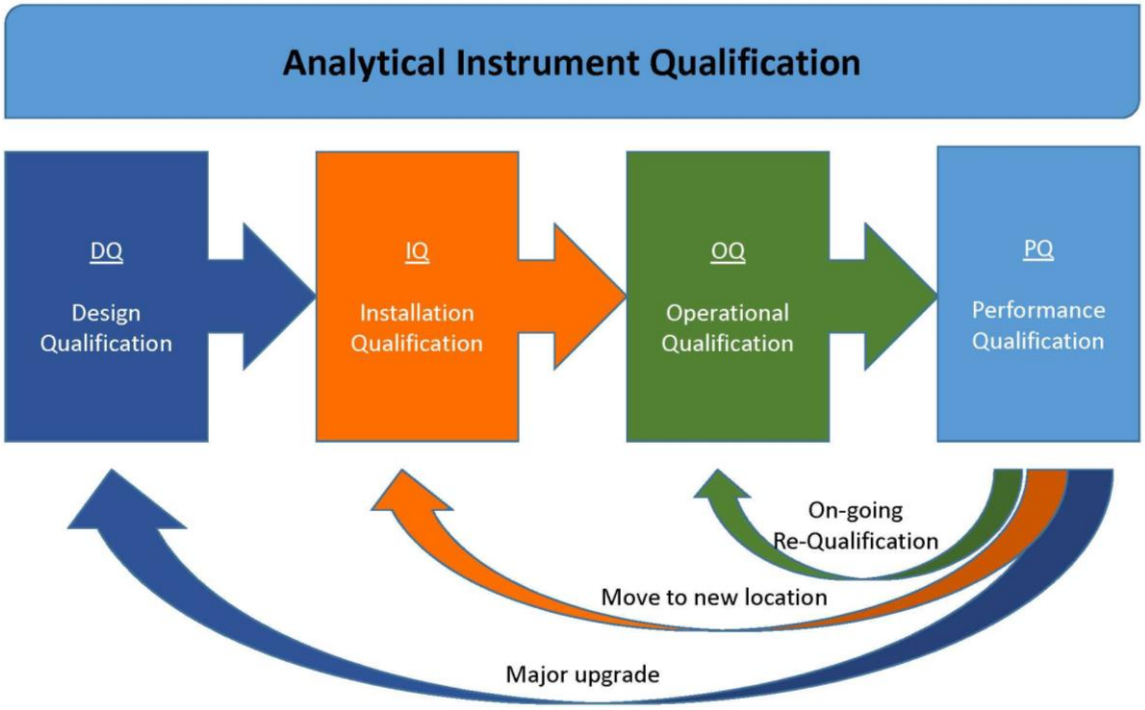

Fig. 9: Analytical instrument qualification in the “4Q model” [141]

After ordering and delivery of the optimal LC instrument or system, the Installation Qualification (IQ) phase starts with the documentation of delivered components, the installation of all LC modules as well as training provided for the users.
During the Operational Qualification (OQ) the LC instrument is tested under standardized conditions so that the correct operations of the instrument in the light of

its specification can be confirmed. Later on the Performance Qualification (PQ) addresses the suitability of the instrument under actual conditions of use and based on good scientific practice [129].

The full 4Q qualification process is performed every time a new instrument is implemented into a laboratory. Requalification of an existing instrument after a specified time period within the lifecycle of the instrument – which is typically linked to preventive maintenance procedures – is necessary to prove that the system is still fit for purpose. In addition, when the location of an instrument has changed or the instrument undergoes major repairs or modifications, relevant IQ, OQ and/or PQ tests should be repeated [130].

According to USP <1058> "*Analytical Instrument Qualification*", laboratory equipment is risk-based categorized in the risk groups A to C to establish the extend of qualification activities necessary to demonstrated fitness for intended use:

Standard laboratory equipment with no measurement capability and no need for calibration are in group A. Qualification processes are not necessary. Examples are magnetic stirrers, evaporators, etc.

Standard laboratory equipment with measurement capability that needs calibration are in group B. Conformance to user requirements are documented during IQ and OQ phases. Examples are balances, pH meters and thermometers.

Group C includes complex instruments and computerized analytical systems. Conformance to user requirement is documented through all qualification phases.
In addition to dissolution testers and spectrometers, all LC systems are classified as category C instruments.

As part of the risk management the classification is used to establish the level of qualification activities necessary to demonstrate fitness for intended use. For example, in HPLC analysis a frequent system suitability test - as required by pharmacopeia chapters European Pharmacopeia (Ph.Eur.) 2.2.46 [131] and USP<621> [132] - can be seen as an ongoing performance qualification for its intended use. Therefore,

trending of system suitability data in control charts helps to identify and understand potential issues and take preventive actions before a major problem occurs [128, 133, 134].

The USP chapter <1058> is of global significance because the USP is the only Pharmacopeia that provides guidance on analytical instrument qualification. In recent years the complexity and sophistication of computerized analytical instruments used for automated laboratory testing and data management has increased significantly and it is necessary to make the USP chapter compatible to Good Automated Manufacturing Practice 5 (GAMP5) for the validation of computerized systems [135, 136]. The revision process for the USP chapter <1058> is on-going and changes will be made to the content before an updated chapter will be finalized [137, 138].

6. Conclusions and future perspectives

The implementation of the ICH guideline Q8 to Q11 [78-81] within the pharmaceutical industry is intended to modernize the current approach for development and manufacturing of pharmaceuticals to a more scientific and risk-based approach.

Although the ICH guideline Q8 does not explicitly mention analytical method development, a Quality-by-Design (QbD) approach in pharmaceutical development is requested [78]. Therefore, the QbD concept may be extended to analytical methods. Stimuli articles to the USP follow this trend [104, 106-108].

In the lifecycle approach for analytical methods, the ATP is the reference point and requirements are defined up-front. The uses of analytical Quality-by-Design tools lead to deeper understanding on how critical variables influence method performance and resulting in more robust and reliable methods. In addition, the lifecycle approach assures that the validation status of the method is always maintained and facilitates continuous improvements [139].

While the concepts in ICH Q8, Q9, Q10 and Q11 provide opportunities for a more science and risk-based approach for assessing changes across the lifecycle, several gaps exist which limit full realization of intended benefits. The envisioned post-approval flexibility has not been achieved yet.
Therefore, a new proposed ICH guideline Q12 [140] will provide guidance to facilitate the management of post-approval changes in a more predictable and efficient manner across the product lifecycle. Adoption of this new ICH Guideline will promote innovation and continuous improvement, and strengthen quality assurance and reliable supply of pharmaceutical products.

In addition, the enrollment of further ICH guidelines and a new chapter of the USP are already discussed to give guidance explicitly to the lifecycle of analytical procedures [104, 139].

7. Publications

7.1. Manuscript No. 1:

"Computer-assisted Optimization in the Development of HPLC Method for the Analysis of Kava Pyrones in Piper methysticum Preparations"

Alexander H. Schmidt, Imre Molnár

Journal of Chromatography A 948 (2002) 51-63.

https://doi.org/10.1016/S0021-9673(02)00066-3

Erratum in Journal of Chromatography A 1110 (2006) 272.

https://doi.org/10.1016/j.chroma.2006.02.022

In this work, the chromatography modeling program DryLab was used to optimize the separation of six kava pyrones and two unidentified components obtaining the best resolution and the shortest run time. With DryLab it was possible to find the best separation conditions without running a large number of possible combination of variables in the laboratory.

Starting with four initial experiments, the software allowed to optimize gradient time t_G and temperature T simultaneously. Changing other variables such as type of organic modifier, the eluent pH, the gradient form, and the flow-rate, the optimization resulted in resolution $R_s > 1.5$ for all kava pyrones and the two additional newly detectable peaks.

The HPLC method may be used to analyze kava pyrones in *Piper methysticum* preparations.

7.2. Manuscript No. 2:

"Development of an HPLC method for the determination of hydroxycinnamic acid derivatives in Cimicifuga racemosa (Black Cohosh) extracts by using an Automated Method Development System"

Alexander H. Schmidt
Journal of Liquid Chromatography & Related Technologies 28 (2005) 871-881
http://dx.doi.org/10.1081/JLC-200051475

The separation of a complex mixture, such as the ingredients in medicinal plants, is typically difficult and the development of a HPLC method is a labor-intensive and time-consuming process if carried out manually. Automation of this process can increase productivity of a pharmaceutical R&D department substantially.

This paper describes the development of a high performance liquid chromatographic method for the determination of hydroxycinnamic acid derivatives in *Cimicifuga racemosa* extracts and its preparations by using a fully automated method development system (Waters AMDS in combination with DryLab modeling software).

The developed method is based on the baseline chromatographic separation of six hydroxycinnamic acid derivatives (caffeic acid, ferulic acid, isoferulic acid, fukinolic acid, cimicifuga acid A, and cimicifuga acid B), the major constituents in *Cimicifuga racemosa* (Black Cohosh), on a XTerra MS C18 column with a water-methanol gradient and photodiode array detection.

7.3. Manuscript No. 3:

Rapid UHPLC Method Development for Omeprazole Analysis in a Quality-by-Design Framework and Transfer to HPLC Using Chromatographic Modeling

Alexander H. Schmidt, Mijo Stanic
LCGC North America, 32 (2014) 126-148

In this paper, a Quality-by-Design based method development strategy for a purity method of omeprazole and its related impurities is presented. The scientific and risk-based multi-factorial method development strategy uses visual chromatographic modeling as a fast and easy to use development tool. To speed up the method development process, all experiments were performed on a UHPLC system. The final method was successfully transferred to HPLC conditions. Verification studies between predicted and experimental retention times confirm the accuracy of the chromatographic modeling process.

7.4. Manuscript No. 4:

A QbD with Design-of-Experiments approach for development of a state-of-the-art UPLC purity method for carbamazepine

Alexander H. Schmidt, Carsten Wess
Journal of Liquid Chromatography and Related Technologies 37 (2014) 2653-2666

http://doi.org/10.1080/10826076.2013.853312

In this work, a state-of-the-art ultra-high performance liquid chromatographic (UHPLC) method has been developed for purity testing of carbamazepine. Successful chromatographic separation of the active pharmaceutical ingredient (API) from its impurities was achieved on a C18 column with the dimensions 2.1mm x 100mm and 1.7 µm particle size with gradient elution of 0.2% phosphoric acid and acetonitrile in only 5 min.

Incorporating Quality-by-Design (QbD) principles to the method development approach by using the statistical software package Fusion AE allows the study of the relationship between chromatographic parameters (factors) and the resolution (response) between the peaks of interest. In a screening phase, the factors known to have a major effect on column selectivity (stationary phase, pH of the aqueous eluent, organic eluent type, gradient time, and slope) were studied. In the second phase, the chromatographic parameters that were identified as affecting the resolution were studied with additional instrument settings. In both phases, statistical concepts with experimental design plans (Design-of-Experiments) are used as an efficient and fast tool to simultaneously gain knowledge regarding the influencing factors and interactions. An operating space within the design space was established and a verification study confirmed the robustness of the final method.

Total analysis time was only 5 min, which is an impressive 22-fold increase in productivity in comparison to the method published in the European Pharmacopeia.

7.5. Manuscript No. 5:

„Using a Quality-by-Design approach for development of a stability indicating UPLC method for ebastine"

Alexander H. Schmidt, Imre Molnár
Journal of Pharmaceutical and Biomedical Analysis 78-79 (2013) 65-74
http://dx.doi.org/10.1016/j.jpba.2013.01.032

In this paper, the development of a stability-indicating ultra high performance liquid chromatographic (UHPLC) method for purity testing of ebastine and its pharmaceutical formulations has been presented. Successful chromatographic separation of the API from impurities was achieved on a C18, 50 mm × 2.1 mm, 1.7 µm particle size column with gradient elution of 10 mM acetate buffer pH 6.2 and a mixture of acetonitrile/2-propanol (1:1) as the mobile phase.

Incorporating Quality-by-Design (QbD) principles to the method development approach by using the chromatography modeling software DryLab allows the visualization of a "Design Space", a region in which changes to method parameters will not significantly affect the results as defined in the ICH guideline Q8(R2). A verification study demonstrated that the established model for Design Space is accurate with a relative error of prediction of only 0.6%.

The method was fully validated for specificity, linearity, accuracy and precision, and robustness in compliance to the ICH guideline Q2(R1). The method was found to be linear in the concentration range from the quantification limit (LOQ) to 125% of the specification limit for ebastine and each of the impurities with correlation coefficients of not less than 0.999. The recovery rate was between 98.15 and 100.30% for each impurity. The repeatability and intermediate precision (RSD) were less than 3.2% for ebastine and each of the impurities.

The robustness of the developed method was studied by varying the six parameters: gradient time, temperature, ternary composition of the eluent, flow rate and start and end concentration of the gradient at 3 levels (+1, 0, −1). The resulting 729 experiments were performed in silico from the previously constructed model for Design Space and

showed that the required resolution of 2.0 can be reached in all experiments. To prove the stability-indicating performance of the method, forced degradation (acid and base hydrolysis, oxidation, photolytic and thermal stress conditions) of ebastine was carried out.

Baseline separation could be achieved for all peaks of the impurities, the degradation products and the API. Total run time was only 4 min, which is an impressive 40-fold increase in productivity in comparison to the method published in the Ph. Eur. monograph and allowed purity testing of more than 360 samples per day.

7.6. Manuscript No. 6:

In silico robustness testing of a compendial HPLC purity method by using of a multidimensional design space build by chromatography modeling – Case study pramipexole

Alexander H. Schmidt, Mijo Stanic, Imre Molnár
Journal of Pharmaceutical and Biomedical Analysis, 91 (2014) 97-107

http://dx.doi.org/10.1016/j.jpba.2013.12.023

Purity testing of the active pharmaceutical ingredient (API) pramipexole is performed using an official (compendial) and harmonized method published in the European Pharmacopeia (E.P.) and United States Pharmacopeia (USP). According to this monograph the successful chromatographic separation of the API from impurities is achieved on a C18 column with gradient elution of an ion pairing buffer of pH 3.0 (mobile phase A) and acetonitrile (mobile phase B). Although not recommended in general, compendial methods are often adapted for purity testing of generic formulations. In this paper a novel approach to evaluate method robustness of an adapted method– prior of full method validation – is described. Based on Quality-by-Design (QbD) principles, a small number of experiments are performed, which after entering them into a chromatography modeling software allow to visualize a multidimensional “Design Space”, a region, in which changes in method parameters will not significantly affect the results as defined in the ICH guideline Q8(R2) leading to a more flexible method handling in routine analysis. For two different recommended C18 columns a multidimensional Design Space (Method Operating Design Region, MODR) was constructed to study the robustness of the adapted method with a newly developed Robustness Module. In a full factorial design the following six parameters were varied at three levels (low, nominal, high): gradient time, temperature, pH of the aqueous eluent (A), flow rate, start- and end concentration of the organic mobile phase component (eluent B). The resulting 36= 729 experiments were performed in silico from the previously constructed models for Design Space in less than 1 min and showed that the required resolution of 2.0 could not be reached in all experiments for the two columns which were recommended by the E.P. (failure rate 25% and 16%,

respectively). However, by adjusting the gradient time, we were able to fulfill the requirements with a failure rate of zero. For the aqueous eluent a separate “Eluent Design Space” study was performed, which allows the construction of ionic strength vs. ion pairing concentration models to identify the optimum combination of the concentrations for the buffer and the ion-pairing reagent.

8. Declaration of Own Contribution

In the following, the author's own contributions to the individual publications, which are the basis for this cumulative work, are presented in detail:

Manuscript No.	conception	data collection	data evaluation	manuscript preparation
1	50%	50%	50%	50%
2	100%	50%	100%	100%
3	100%	25%	75%	100%
4	100%	25%	75%	100%
5	100%	25%	75%	75%
6	100%	25%	75%	75%

9. References

[1] S.A.C. Wren, P. Tchelitcheff. Use of UPLC in pharmaceutical analysis. J Chromatogr A 1119 (2006) 140-146.

[2] L.R. Snyder. HPLC Past and Present. Anal Chem 72 (2000) 412A-420A.

[3] J.J. Kirkland (Ed.). Modern Practice of Liquid Chromatography. Wiley-Interscience, New York (1971).

[4] L.R. Snyder, J.J. Kirkland, J.L. Glajch. Practical HPLC Method Development. 2nd ed., Wiley-Interscience, New York (1997).

[5] L.R. Snyder, J.L. Glajch. Computer-assisted Method Development for High Performance Liquid Chromatography. Elsevier, Amsterdam (1990).

[6] J.B. Crowther, W. Lauwers, S. Adusumalli, P. Shenbagamurthi. The Laboratory Analyst's Role in the Drug Development Process. In: J.M. Miller, J.B. Crowther (Eds.). Analytical Chemistry in a GMP Environment. A Practical Guide. John Wiley, New York (2000) 448-449.

[7] Molnár-Institute. DryLab User's Manual, Chapter 8 – Developing a Method. (2006) 159-177.

[8] S. Fletcher. Is the Art von HPLC Method Development Dead ? Chromatograhy Today Nov/Dec (2013) 28-30.

[9] U.D. Neue. HPLC Columns – Theory, Technology, and Practice. Wiley-VCH, Weinheim, (1997).

[10] Beginners Guide to UPLC. Waters Corp., Milford (2009).

[11] M.W. Dong. Modern HPLC for Practicing Scientists. Wiley-Interscience, New Jersey (2006).

[12] M.E. Swartz. Contemporary liquid chromatographic systems for method development. In: HPLC Method Development for Pharmaceuticals, S. Ahuja, H. Rasmussen (Eds.) Elsevier, Amsterdam (2007) 145-187.

[13] L.R. Snyder, J.W. Dolan, P.W. Carr. The "Hydrophobic-subtraction" Model of Reversed-phase Column Selectivity. J Chromatogr A 1060 (2004) 77-116.

[14] L.R. Snyder, J.W. Dolan, P.W. Carr. A New Look at the Selectivity of Reversed-phase HPLC Columns. Anal Chem 79 (2007) 3255-3261.

[15] L.R. Snyder , A. Maule, A. Heebsch, R. Cuellar, S. Paulson, J. Carrano, L. Wrisley, C.C. Chan, N. Pearson, J.W. Dolan, J. Gilroy. A fast, convenient and rugged procedure for characterizing the selectivity of alkyl-silica columns. J Chromatogr A 1057 (2004) 49-57.

[16] J.W. Dolan, A. Maule, L. Wrisley,, C.C. Chan, M. Angod, C. Lunte, R. Krisko, J. Winston, B. Homeierand, D.M. McCalley, L. R.Snyder. Choosing an equivalent replacement column for a reversed-phase liquid chromatographic assay procedure. J Chromatogr A 1057 (2004) 59-74.

[17] B. Bidlingmeyer, C.C. Chan, P. Fastino, R. Henry, P. Koerner, A. Maule, M.R.C. Marques, U.D. Neue, L. Ng, H. Pappa, L. Sander, C. Santasania, L. Snyder, T. Woznaik. Stimuli to the Revison Process: HPLC Column Classification. Pharmacopeial Forum 31 (2005) 637–645.

[18] M.E. Swartz. Ultra Performance Liquid Chromatography (UPLC): An Introduction. LC GC North America 23 (Suppl.) (2005) 8-14.

[19] A. D. Jerkovich, R. LoBrutto, R. V. Vivilecchia. The Use of ACQUITY UPLC in Pharmaceutical Development. LC GC North America 23 (Suppl.) (2005) 15-21.

[20] M.E. Swartz, B. Murphy. UPLC: An introduction and review. J Liq Chromatogr Relat Technol 28 (2005) 1253-1263.

[21] J.R. Mazzeo, U.D. Neue, M. Kele, R.S. Plumb. A new separation technique takes advantage of sub-2- µm porous particles. Anal Chem 77 (2005) 460A-467A.

[22] S. Ahuja, M.W. Dong. Handbook of Pharmaceutical Analysis by HPLC. Vol. 6, Elsevier, Amsterdam (2005).

[23] P.D. McDonald. The Quest for Ultra Performance in Liquid Chromatography: Origins of UPLC Technology, Waters Corp., Milford (2009).

[24] D.T.-T. Nguyen, D. Guillarme, S. Rudaz, J.-L. Veuthey. Fast analysis in liquid chromatography using small particle size and high pressure. J Sep Sci 29 (2006) 1836-1848.

[25] M. Swartz. Recent Developments in HPLC/UHPLC. Chromatogrohyonline.com, Special Issue Apr 1 (2011).

[26] M.W. Dong, K. Zhang, Ultra-high-pressure liquid chromatography (UHPLC) in method development, Trends in Anal Chem 63 (2014) 21-30.

[27] M. Gumustas, S. Kurbanoglu, B. Uslu, S. Kurbanoglu. UPLC versus HPLC on Drug Analysis: Advantageous, Application and Their Validation Parameters. Chromatographia 76 (2013) 1365-1427.

[28] L.R. Snyder. Efficient HPLC Method Development and Personal Reflections. LC GC Europe 25 (2012) 437-444.

[29] R. Kormany, H.-J. Rieger, I. Molnár. Application of Quality by Design Principles to a Pharmaceutical Sample Using UHPLC Method Development with Modeling Technologies. Chromatographyonline.com, October (2013).

[30] A.H. Schmidt, I. Molnár. Using an innovative Quality-by-Design approach for development of a stability indicating UHPLC method for ebastine in the API and pharmaceutical formulations. J Pharm Biomed Anal 78-79 (2013) 65-74.

[31] A.H. Schmidt. Course manuscript “Quality-by-Design in analytical method development” organized by Molnár Institute, Berlin, Germany (2012).

[32] R. Peraman, K. Bhadraya, Y.P. Reddy. Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analytics. Int J Anal Chem 2015 (2015) 868727.

[33] B. Nickerson (ed.), Sample Preparation of Pharmaceutical Dosage Forms, Springer, Heidelberg, 2011.

[34] R.E. Majors. Overview of Sample Preparation. LC GC 9 (1991) 16-20.

[35] L. Ramos. Critical overview of selected contemporary sample preparation techniques. J Chromatogr A 1221 (2012) 84-98.

[36] M.S. Chang, Q. Ji, J. Zhang, T.A. El-Shourbagy. Historical review of sample preparation for chromatographic bioanalysis: pros and cons. Drug Develop Res 68 (2007) 107–133.

[37] Analytical Method Development for Assay and Impurity Determination in Drug Substances and Drug Products. In: J.M. Miller, J.B. Crowther (Eds.): Analytical Chemistry in a GMP Environment. A Practical Guide, John Wiley, New York (2000) 331-370.

[38] D.B. Hibbert. Experimental design in chromatography: A tutorial review. J Chromatogr B 910 (2012) 2-13

[39] W.A. Wan Raihana, Optimization of Analytical Methods Using Factorial Designs, Part 1: An Introduction. Separation Science 4(4) (2012) 10-14.

[40] W.A. Wan Raihana, Optimization of Analytical Methods Using Factorial Designs, Part 2: A Deeper Look at Factoral Designs. Separation Science 4(6) (2012) 14-16.

[41] R.L. Plackett, J.P. Burman. The Design of Optimum Multifactorial Experiments. Biometrika 33 (1946) 305-325.

[42] A.B. Baranda, N. Etxebarria, R.M. Jimenez, R.M. Alonsa. Improvement of the Chromatographic Separation of several 1,4-Dihydropyridines Calcium Channel Antagonist Dugs by Experimental Design. J Chromatogr Sci. 43 (2005) 505-512.

[43] S. Karmarkar, R. Garber, Y. Genchanok, S. George, X. Yang, R. Hammond. Quality by Design (QbD) Based Development of a Stability Indicating HPLC Method for Drug and Impurities. J Chromatogr Sci 49 (2011) 439-446.

[44] E. Rozet, P. Lebrun, B. Debrus, P. Hubert. New methodology for the development of chromatographic methods with bioanalytical application. Bioanalysis 4 (2012) 755-758.

[45] G.E.P. Box, D.W. Behnken. Simplex-Sum Designs: A Class of Second Order Rotatable Designs Derivable From Those of First Order. Ann Math Stat 31 (1960) 838-864.

[46/] S.L. Ferreira, R.E. Bruns, H.S. Ferreira, G.D. Matos, J.M. David, G.C. Brandão, E.G. da Silva, L.A. Portugal, P.S. dos Reis, A.S. Souza, W.N.L. dos Santos. Box-Behnken design: an alternative for the optimization of analytical methods. Anal Chim Acta 597 (2007) 179-186.

[47] R. Bade, L. Bijlsma, J.V. Sancho, F. Hernandez. Critical evaluation of a simple retention time predictor based on LogKow as a complementary tool in the identification of emerging contaminants in water. Talanta 139 (2015) 143-149.

[48] T.H. Miller, A. Musenga, D.A. Cowan, L.P. Barron. Prediction of chromatographic retention time in high-resolution anti-doping screening data using artificial neural networks. Anal Chem 85 (2013) 10330-10337.

[49] S. Agatonovic-Kustrin, M. Zecevic, L. Zivanovic. Use of ANN modelling in structure--retention relationships of diuretics in RP-HPLC. J Pharm Biomed Anal 21 (1999) 95-103.

[50] F:Y. Chen, X.W. Cao, S:Y. Han, H.Z. Lian, L. Mao. Relationship between hydrophobicity and RPLC retention behavior of amphoteric compounds. J Liq Chromatogr Relat Technol 37 (2014) 2711-2724.

[51] M. Talebi, S.H. Park, M. Taraji, Y. Wen, R,I.J. Amos, P.R. Haddad, R.A. Shellie, R. Szucs, C.A. Pohl, J.W. Dolan. Retention Time Prediction Based on Molecular Structure in Pharmaceutical Method Development: A Perspective. LCGC North America 34 (2016) 550–558.

[52] M. Goodarzi, R. Jensen, Y. V. Heyden. QSRR modeling for diverse drugs using different feature selection methods coupled with linear and nonlinear regressions. J Chromatogr B 910 (2012) 84-94.

[53] J. M. Pallicer, C. Calvet, A. Port, M. Rosés, C. Ràfols, E. Bosch. Extension of the liquid chromatography/quantitative structure–property relationship method to assess the lipophilicity of neutral, acidic, basic and amphotheric drugs. J Chromatogr A 1240 (2012) 113-122.

[54] K. Muteki, J.E. Morgado, G.L. Reid, J. Wang, G. Xue, F.W. Riley, J.W. Harwood, D.T. Fortin, I.J. Miller. Quantitative Structure Retention Relationship Models in an Analytical Quality by Design Framework: Simultaneously Accounting for Compound Properties, Mobile-Phase Conditions, and Stationary-Phase Properties. Ind Eng Chem Res 52 (2013) 12269-12284.

[55] M.R. Euerby, M. Fever, J. Hulse, M. James, P. Petersson, C. Pipe. Maximization of Selectivity in Reversed-Phase Liquid Chromatographic Method Development Strategies. LC GC Europe 29 (2016) 8-21.

[56] R. Verseput, J.A. Turpin. Fusion QbD and the “Perfect Storm” of Technologies Driving QbD aligned LC Method Development. Chromatography Today, Aug./Sept (2015) 64-68.

[57] W.-D. Beinert, V. Eckert, S. Galushko, V. Tanchuk, I. Shishkina. Automated HPLC Method Development: A Step Forward with Innovative Software Technology. LC GC Europe 14 (2001) 34-38.

[58] I. Molnár. Computerized design of separation strategies by reversed-phase liquid chromatography: development of DryLab software. J Chromatogr A 965 (2002) 175-194.

[59] I. Molnár, H.-J. Rieger, K.E. Monks. Aspects of the “Design Space” in High Pressure Liquid Chromatography Method Development. J Chromatogr A 1217 (2010) 3193–3200.

[60] L.R. Snyder, J.L. Glajch. Computer-assisted Method Development for High Performance Liquid Chromatography. Elsevier, Amsterdam (1990) (also J. Chromatogr. A 485 (1989) 1-675).

[61] J.W. Dolan, L.R. Snyder, T. Blanc, L. Van Heukelem. Selectivity differences for C18 and C8 reversed-phase columns as a function of temperature and gradient steepness, I. Optimizing selectivity and resolution. J Chromatogr A 897 (2000) 37-50.

[62] J.W. Dolan, L.R. Snyder, T. Blanc. Selectivity differences for C18 and C8 reversed-phase columns as a function of temperature and gradient steepness, II. Minimizing column reproducibility problems. J Chromatogr A 897 (2000) 51-63.

[63] I. Molnár. Computerized design of separation strategies by reversed-phase liquid chromatography: development of DryLab software. J Chromatogr A 965 (2002) 175-194.

[64] I. Molnár, K.E. Monks. From Csaba Horváth to Quality by Design: Visualizing Design Space in Selectivity Exploration of HPLC Separations. Chromatographia 73 (2011), Suppl.1, 5-14.

[65] K. Jayaraman, A.J. Alexander, Y. Hu, F.P. Tomasella. A stepwise strategy employing automated screening and DryLab modeling for the development of robust methods for challenging high performance liquid chromatography separations: A case study. Anal Chim Acta 696 (2011) 116-124.

[66] K. Monks, I. Molnár, H.-J. Rieger, B. Bogáti, E. Szabó. Quality by Design: Multidimensional Exploration of the Design Space in High Performance Liquid Chromatography Method Development for better Robustness before Validation. J Chromatogr A 1232 (2012) 218-230.

[67] R. Kormány, I. Molnár, J. Fekete. Quality by Design in Pharmaceutical Analysis Using Computer Simulation with UHPLC. LC GC Europe 27 (2014) 240-248.

[68] M. McBrian. Practical Implications of Quality by Design to Chromatographic Method Development. Chromatography Today 3 (2010) 30-34.

[69] M. Swartz, I. S. Krull, J. Turpin, P. H. Lukulay, R. Verseput. A Quality-by-Design Methodology for Rapid LC Method Development, Part III. LC GC North America 27 (2009) 328–339.

[70] A.H. Schmidt, I. Molnár. Computer-assisted optimization in the development of a high-performance liquid chromatographic method for the analysis of kava pyrones in Piper methysticum preparations. J Chromatogr 948 (2002) 51-63.

[71] A.H. Schmidt. Development of an HPLC method for the determination of hydroxycinnamic acid derivates in Cimicifuga racemosa (black cohosh) extracts using an automated method development system. J Liq Chromatogr Relat Technol 28 (2005) 871-881.

[72] B. Debrus, P. Lebrun, A. Ceccato, G. Caliaro, E. Rozet, I. Nistor, R. Oprean, F.J. Rupérez, C. Barbas, B. Boulanger, P. Hubert. Application of new methodologies based on design of experiments, independent component analysis and design space for robust optimization in liquid chromatography. Anal Chim Acta 691 (2011) 33-42.

[73] H.I. Mokhtar, R.A. Abdel-Salam. Design Space Calculation by In Silico Robustness Simulation with Modeling Error Propagation in QbD framework of RP-HPLC method development. Chromatographia 78 (2015) 457-466.

[74] FDA's Pharmaceutical cGMPs for the 21st Century — A risk-based approach. Final Report September 2014. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM176374.pdf

[75] Staff Reporter. Pharmaceutical Trouble in the making: Sloppy manufacturing comes under fire, but inefficiency is the real problem. The Economist, Aug. 28 (2002).

[76] J. Carey, M. Arndt. Making pills the smart way. Business Week, May 3 (2004) 102-103.

[77] P. Nethercote, J. Ermer. Analytical Validation within the Pharmaceutical Lifecycle, In: Method Validation in Pharmaceutical Analysis. A Guide to Best Practice. 2nd Edition, J. Ermer, P. Nethercote (Eds.), Wiley VCH, Weinheim (2015).

[78/] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Q8(R2): Pharmaceutical development (2009). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

[79] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Q9: Quality Risk Management (2005). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

[80] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Q10: Pharmaceutical Quality System (2008). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

[81] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (2012). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

[82] J.M.Juran. Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services. The Free Press, New York (1992).

[83] J. Terzic, I. Popovic, A. Stajic, A. Tumpa, B. Jancic-Stojanovic. Application of Analytical Quality by Design concept for bilastine and its degradation impurities determination by hydrophilic interaction liquid chromatographic method. J Pharm Biomed Anal 125 (2016) 385-393.

[84] J. Kochling, W. Wu, Y. Hua, Q. Guan, J. Castaneda-Merced. A platform analytical quality by design (AQbD) approach for multiple UHPLC-UV and UHPLC-MS methods development for protein analysis. J Pharm Biomed Anal 125 (2016) 130-139.

[85] E. van Tricht, L. Geurink, H. Backus, M. Germano, G.W. Somsen, C.E. Sanger-van de Griend. One single, fast and robust capillary electrophoresis method for the direct quantification of intact adenovirus particles in upstream and downstream processing samples. Talanta 166 (2017) 8-14.

[86] R.K. Khurana, S. Rao, S. Beg, O.P. Katare, B. Singh. Systematic Development and Validation of a Thin-Layer Densitometric Bioanalytical Method for Estimation of Mangiferin Employing Analytical Quality by Design (AQbD) Approach. J Chromatogr Sci 54 (2016) 829-841.

[87] A. Tumpa, A. Stajic, B. Jancic-Stojanovic, M. Medenica. Quality by Design in the development of hydrophilic interaction liquid chromatography method with gradient elution for the analysis of olanzapine. J Pharm Biomed Anal 134 (2017) 18-26.

[88] M. Shivhare, G. McCreath. Practical Considerations for DoE Implementation in Quality By Design. BioProcess Int June (2010) 22-30.

[89] Course Manuscript “Quality by Design in Pharmaceutical Analysis”, organized by European Compliance Academy in Barcelona, Spain (2012).

[90] M. Hanna-Brown, R. Szucs, B. Harrington. Method Design and Understanding. In: Method Validation in Pharmaceutical Analysis. A Guide to Best Practice. 2nd Edition, J. Ermer, P. Nethercote (Eds.), Wiley VCH, Weinheim (2015).

[91] X.-T. Sun, Q.-J. Tan, S.-X. Wang, J.-F. Shan, J.-L. Jiang. Systematic, compute-assisted development of high performance liquid chromatography for multi-component analysis. Analytical Methods 7 (2015) 5428-5435.

[92] K. Barnett, K. Doyle, K. Wang, J. Morgado, J. Harwood. Applying Quality by Design Principles to Analytical Methods to Gain Enhanced Method Understanding. American Pharmaceutical Review.com, May 18 (2015).

[93] K.E. Monks, H.-J. Rieger, I. Molnár. Expanding the term “Design Space” in high performance liquid chromatography (I). J Pharm Biomed Anal 56 (2011) 874-879.

[94] G.L. Reid, G. Cheng, D.T. Fortin, J.W. Harwood, J.E. Morgado, J. Wang, G. Xue. Reversed-phase liquid chromatographic method development in an analytical quality by design framework. J Liq Chromatogr Relat Technol 36 (2013) 2612-2638.

[95] C. Hubert, S. Houari, E. Rozet, P. Lebrun, P. Hubert. Towards a full integration of optimization and validation phases: An analytical-quality-by-design approach. J Chromatogr A 1395 (2015) 88-98.

[96] H. Bhutani, M. Kurmi, S. Singh, S. Beg, B. Singh. Quality by Design (QbD) in Analytical Sciences: An Overview. Pharma Times 46 (8) (2014) 71-75.

[97] N.S. Thakor, S.V. Amrutkar. Implementing Quality by Design (QbD) in Chromatography. Austin J Anal Chem 4(1) (2017) 1078.

[98] N.V.V.S.S. Raman, U.R. Mallu, H.R. Bapatu. Analytical Quality by Design Approach to Test Method Development and Validation in Drug Substance Manufacturing. J Chem 2015 (2015) 8 pages.

[99] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Q2(R1): Validation of Analytical Procedures: Text and Methodology (2005). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1_Guideline.pdf

[100] I. Molnár. Course Manuscript “Quality by Design Principles for the Development of Analytical HPLC Methods” organized by Molnár-Institute, Berlin, Germany (2011).

[101] R.D. Dowell. Lifecycle and Quality by Design for Chromatographic Methods. LC GC Europe 27 (2014) 91-97.

[102] J. Ermer. Quality by Design: A Lifecycle Concept for Pharmaceutical Analysis. European Pharmaceutical Review 16 (2011) 32-39.

[103] G.P. Martin, K.L. Barnett, C. Burgess, P.D. Curry, J. Ermer, G.S. Gratzl, J.P. Hammond, J. Herrmann, E. Kovacs, D.J. LeBlond, R. LoBrutto, A.K. McCasland-Keller, P.L. McGregor, P. Nethercote, A.C. Templeton, D.P. Thomas, J. Weitzel. Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification. Pharmacopeial Forum 39(5) (2013).

[104] G.P. Martin, K.L. Barnett, C. Burgess, P.D. Curry, J. Ermer, G.S. Gratzl, J.P. Hammond, J. Herrmann, E. Kovacs, D.J. LeBlond, R. LoBrutto, A.K. McCaslandKeller, P.L. McGregor, P. Nethercote, A.C. Templeton, D.P. Thomas, J. Weitzel, H. Pappa. Stimuli to the Revision Process: Proposed New USP General Chapter: The Analytical Procedure Lifecycle ⟨1220⟩. Pharmacopeial Forum 43(1) (2016).

[105] FDA. Guidance for Industry on Process Validation: General Principles and Practices (2011) https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

[106] C. Burgess, P. Curry, D.J. LeBlond, G.S. Gratzl, E. Kovacs, G.P Martin, P.L. McGregor, P. Netthercote, H. Pappa, J. Weitzel. Stimuli to the Revision Process: Fitness for Use: Decision Rules and Target Measurement Uncertainty. Pharmacopeial Forum 42(2) (2016).

[107] K.L. Barnett, O.L. McGregot, G.R. Martin, D.J. LeBlond, M.L.J. Weitzel, J. Ermer, S. Walfish, P. Nethercote, G.S. Gratzl, E. Kovacs. Stimuli to the Revision Process: Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle. Pharmacopeial Forum 42(5) (2016).

[108] E. Kovacs, J. Ermer, P. McGregor, P. Nethercote, R. LoBrutto, G.P. Martin, H. Pappa. Stimuli to the Revision Process: Analytical Control Strategy. Pharmacopeial Forum 42(5) (2016).

[109] M. Hanna-Brown, K. Barnett, B. Harrington, T. Graul, J. Morgado, S. Colgan, L. Wrisley, R. Szucs, G. Sluggett, G. Steeno, J. Pellett. Using Quality by Design to Develop Robust Chromatographic Methods. Pharm Technol Europe 38 (2014) 70-88.

[110] M.L.J. Weitzel. Establishment of Measurement Requirements – Analytical Target Profile and Decicion Rules. In: Method Validation in Pharmaceutical Analysis. A Guide to Best Practice. 2nd Edition, J. Ermer, P. Nethercote (Eds.), Wiley VCH, Weinheim (2015).

[111] American Society of Mechanical Engineers (ASME): Guideline for Decision Rules: Considering Measurement Uncertainty in Determining Conformance to Specifications. Document B89.7.3.1 (2001).

[112] S.L.R Ellison, A. Williams (Eds). Eurachem/CITAC guide: Use of uncertainty information in compliance assessment. First Edition (2007).

[113] International Organization for Standardization. ISO/IEC Guide 98-3, 2008: Uncertainty of measurement -- Part 3: Guide to the expression of uncertainty in measurement (GUM:1995). Geneva (2008).

[114] O.G. Bhusnure, S.B. Gholve, R.N. Suryawanshi, R.V. Sugave, J.N. Sangshetti. Life cycle assessment (LCA) approach to analytical method development: a review. World J Pharmacy Pharm Sci 4 (2015) 933-963.

[115] J. Ermer, H.-J. Ploss: Validation in Pharmaceutical Analysis Part II: Central importance of precision to establish acceptance criteria and for verifying and improving the quality of analytical data. J Pharm Biomed Anal 37(5) (2005) 859-870.

[116] J. Ermer. Examining the concept of validation lifecycle management of analytical procedures. Informa Life Sciences' 4th annual Analytical Method Development, Validation and Transfer conference, DE-Berlin (2014).

[117] P. Nethercote, J. Ermer: Quality by Design for Analytical Methods: Implications for Method Validation and Transfer. Pharm Technol 36(10) (2012) 74-79.

[118] J. Ermer, P.J. Borman, J. Carolan, P. Faulkner, C. Finkler, 0. Grosche, M. HannaBrown, J. Hoffmann, I. Gill, A. Lenhart, P.W. Nethercote, A. Rignall, T. Sokoliess, G. Wegener, M. Pohl. „Quality by Design" bei analytischen Verfahren. Konsequenzen und Möglichkeiten. Pharm Ind 72(2) (2010) 256-264.

[119] M. Schweitzer, M. Pohl, M. Hanna-Brown, P. Nethercote, P. Borman, G. Hansen, K. Smith, J. Larew, J. Carolan, J. Ermer, P. Faulkner, C. Finkler, I. Gill, 0. Grosche, J. Hoffmann, A. Lenhart, A. Rignall, T. Sokoliess, G. Wegener: Implications and Opportunities of Applying QbD Principles to Analytical Measurements. Pharm Technol 24(2) (2010) 52-59.

[120] Pharmaceutical Research and Manufactures of America (PhRMA), Analytical Technical Group (ATG) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), and Analytical Design Space (ADS) topic team. Implications and opportunity of applying QbD principles to analytical measurements. Pharm Technol 24(2) (2010) 29-37.

[121] J. Ermer, M. Limberger, K. Lis, H. Wätzig. The transfer of analytical procedures. J Pharm Biomed Anal 85 (2013) 262 – 276.

[122] C. Agut, A. Caron, C. Giordano, D. Hoffman, A. Segalini. Transfer of analytical procedures: A panel of strategies selected for risk management, with emphasis on an integrated equivalence-based comparative testing approach. J Pharm Biomed Anal 56 (2011) 293-303.

[123] USP 40 – NF 35, <1224> Transfer of Analytical Procedures. United States Pharmacopeial Convention, Rockville, Md., (2017) 1778-1780.

[124] USP 40 – NF 35, <1225> Validation of Compendial Procedures. United States Pharmacopeial Convention, Rockville, Md., (2017) 1780-1785.

[125] USP 40 – NF 35, <1010> Analytical Data-Interpretation and Treatment. United States Pharmacopeial Convention, Rockville, Md., (2017) 836-851.

[126] J. Ermer, C. Arth, P. De Raeve, D. Dill, H.D. Friedel, H. Höwer-Fritzen, G. Kleinschmidt, G. Köller, H. Köppel, M. Kramer, M. Maegerlein, U. Schepers, H. Wätzig. Precision from drug stability studies. Investigation of reliable

repeatability and intermediate precision of HPLC assay procedures. J Pharm Biomed Anal 38(4) (2005) 653-663.

[127] B. Magnusson, U. Örnemark (eds.) Eurachem Guide: The Fitness for Purpose of Analytical Methods – A Laboratory Guide to Method Validation and Related Topics, 2.ed. (2014). Available from www.eurachem.org.

[128] USP 40 – NF 35, <1058> Analytical Instrument Qualification. United States Pharmacopeial Convention, Rockville, Md., (2017) 1137-1143.

[129] P. Smith, R.D. McDowall. Life Cycle Risk Assessment of HPLC Instruments. LC GC Europe 28 (2015) 110-117.

[130] L. Kaminski, J. Ermer, C. Feußner, A. Groh, H. Höwer-Fritzen, P. Link, B. Renger, M. Tegtmeier, H. Wätzig, R.D. McDowall. Why system suitability tests are not a substitute for analytical instrument qualification (Part 3): Performance Qualification (PQ). LC GC Europe 24(8) (2011) 418-422.

[131] European Pharmacopoeia. 8. Nachtrag zur 8. Ausgabe. Kap. 2.2.46 Chromatographische Trennmethoden. Council of Europe. Strasbourg (2016).

[132] USP 40 – NF 35, <621> Chromatography. United States Pharmacopeial Convention, Rockville, Md., (2017) 508-520.

[133] C. Burgess, R.D. McDowall. Analytical Instrument Qualification. In: Method Validation in Pharmaceutical Analysis. A Guide to Best Practice. 2nd Edition, J. Ermer, P. Nethercote (Eds.), Wiley VCH, Weinheim (2015).

[134] L. Kaminski, M. Degenhardt, J. Ermer, C. Feußner, H. Höwer-Fritzen, P. Link, B. Renger, M. Tegtmeier, H. Wätzig. Efficient and economic HPLC performance qualification. J Pharm Biomed Anal 51 (2010) 557-564.

[135] C. Burgess, R.D. McDowall. Stimuli to the Revision Process: An Integrated and Harmonized Approach to Analytical Instrument Qualification and Computerized System Validation - A Proposal for an Extension of Analytical Instrument Qualification <1058>. Pharmacopeial Forum 38(1) (2011).

[136] L. Vuolo-Schuessler, M.E. Newton, P.Smith, C. Burgess, R.D. McDowall. Harmonizing USP <1058> and GAMP for Analytical Instrument Qualification. Pharm Eng 34(1) (2014).

[137] ISPE GAMP Good Practice Guide: A Risk-Based Approach to GyP Compliant Laboratory Computerized Systems, International Society for Pharmaceutical Engineering (ISPE), Second Edition (2012).

[138] First Supplement to USP 40 – NF 35, <1058> Analytical Instrument Qualification. United States Pharmacopeial Convention, Rockville, Md., (2017) 8083-8090.

[139] Course Manuscript “New USP & FDA Approaches for HPLC”, organized by European Compliance Academy, Hamburg, Germany (2017).

[140] ICHQ12 International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, Final Concept Paper Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (2014).

[141] M.K. Parr, A.H. Schmidt. Life cycle management of analytical methods (Review). J Pharm Biomed Anal (2017) in press.

10. Selbstständigkeitserklärung

Hiermit versichere ich, die vorliegende kumulative Dissertation selbstständig und ohne unerlaubte Hilfe angefertigt zu haben. Bei der Verfassung der Dissertation wurden keine anderen als die im Text aufgeführten Hilfsmittel verwendet.

Ein Promotionsverfahren wurde zu keinem früheren Zeitpunkt an einer anderen Hochschule oder bei einem anderen Fachbereich beantragt.

Berlin, den 01. August 2017.

Alexander Schmidt

11. Anhang

11.1. List of Figures

11.2. List of Abbreviations

API	active pharmaceutical ingredient
AQbD	analytical quality-by-design
ASME	American Society of Mechanical Engineers
ATP	analytical target profile
DoE	design of experiments
DQ	design qualification
DS	design space
FDA	US Food and Drug Administration
FMEA	failure mode effect analysis
GMP	Good Manufacturing Practice
HETP	Height equivalent to theoretical plate
HILIC	hydrophilic interaction liquid chromatography
HPLC	high performance liquid chromatography
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IQ	installation qualification
ISO	International Organization for Standardization
LC	liquid chromatography
MODR	method operable design region
OFAT	one-factor-at-a-time
OQ	operational qualification
Ph.Eur.	European Pharmacopeia
PM	prioritization matrix
PQ	performance qualification
PQRI	Product Quality Research Institute
QbD	quality-by-design
QRM	quality risk management
QSAR	quantitative structure activity relationship

QSPR	quantitative structure property relationship
QSRR	quantitative structure-retention relationship
QTPP	quality target product profile
RP	reversed phase
TMU	target measurement uncertainty
UHPLC	ultra high performance liquid chromatography
URS	User Requirement Specification
USP	United States Pharmacopeia

12. Curriculum Vitae including list of publications

„Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten“

„Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten“