

QUALITY BY DESIGN FOR ANALYTICAL METHODS

Jasmina Šljivić¹ Aleksandra Mesarović² Zerina Ibrahimović³

Abstract: The concept of quality by design (QbD) approach provided the opportunity for development of analytical methods and it presents analytical QbD (AQbD). Implementation of AQbD is current trend in pharmaceutical industry. AQbD provides knowledge about the influence of critical process parameters (CPPs) on analytical performances, which are measured using critical quality attributes (CQAs). This multivariate approach provides optimal working area considering all possible interactions between CPPs. The most important part of this concept is the definition of design space (DS). Assurance of quality is guaranteed in this region. The aim of this paper is to outline the significance of this concept in pharmaceutical quality assurance system and its advantages in robust analytical separation method development. Risk assessment methodology and design of experiments are used to ensure that quality would be incorporated into the method. These tools enhance identification and interpretation of the influence of variables on method performance.

Key words: analytical method development, quality assurance, quality by design, robustness, regulatory flexibility, design of experiments, design space

1. INTRODUCTION

Despite the tremendous progress of science, analytical method development approach is still significant challenge. Analytical quality by design (AQbD) is chemometric approach which ensures the robustness of developed method. Modern trends in pharmaceutical industry strongly encourage the implementation of AQbD, which is indicated through different initiatives and regulatory documentation [1]-[5].

The aim of this concept is to improve the quality, efficiency and flexibility in the regulatory sense. It is important to build the quality into the product and to understand the influence of numerous variables on the overall quality [6].

QbD concept is a systematic approach for development with predefined objectives. This approach highlights the understanding of the product and the process [7]. Pharmaceutical industry is challenged with results which are out-of-trend, out-of-specification, out-of-control and out-of-statistical-control. In order to resolve these issues, new strategies are extremely welcome [8].

First phase of AQbD concept is identification of required performances of developed analytical method and identification of the most significant method parameters and attributes of quality. The next phase relates to method optimization, risk assessment and definition of design space (DS). Control strategy must be implemented in order to track method improvements.

AQbD concept is also used for the monitoring of different impurities in drug substances and products. Impurity profile is of key importance for quality control. AQbD approach was successfully applied for understanding and risk management of these methods, with the use of design of experiments methodology and DS [9].

2. DEFINITION OF QUALITY TARGET PRODUCT PROFILE AND SPECIFIC CRITICAL QUALITY ATTRIBUTES

Development of AQbD starts with the concrete definition of the analytical target profile (ATP) which relates to a set of different criteria. It defines where and what will be measured, it specifies concentration without specification of the exact method. ATP defines required performance criteria or critical quality attributes (CQAs).

¹Assistant professor, "Bijeljina" University, Faculty of Pharmacy, Pavlovića put 024, 76 311 Dijelovi, Bijeljina, Bosnia and Herzegovina, jasminasljivic86@gmail.com

²Assistant professor, "Bijeljina" University, Faculty of Pharmacy, Pavlovića put 024, 76 311 Dijelovi, Bijeljina, Bosnia and Herzegovina, krsmanovic.sandra88@gmail.com

³Master of Pharmacy, Vitalpharm d.o.o., Bosanski put bb, 71 000 Sarajevo, Bosnia and Herzegovina, zerina.ibrahimovic@vitalpharm.ba

Quality target product profile (QTPP) presents a summary of all quality product characteristics that would be ideally achieved in order to ensure desired level of quality. For analytical methods, it demands the exact definition of separation criteria (maximal selectivity with minimal total run time in robust working area). CQAs are defined as physical, chemical, biological or microbiological characteristics which should be maintained in defined limit, range or distribution in order to guarantee the desired quality of the product. CQAs for analytical methods are response variables (resolution of the critical pair, retention factor, total run time, separation criteria, precision, and robustness) [6]-[7].

3. DEFINITION OF CRITICAL PROCESS PARAMETERS

The next step is the risk assessment of the method. It is important to identify, classify and relate all potential variables with the requirements which are the part of ATP. Instrumental parameters marked as those of high-risk present critical process parameters (CPPs) and they can be additionally evaluated with the use of design of experiments methodology.

Parameters whose level of variability impacts CQAs are defined as CPPs. These parameters need to be controlled in order to obtain the desired quality and they can be unclassified, critical and non-critical. Quality risk assessment is a process which helps to navigate the identification of CPP, so numerous parameters can be eliminated. After conducted quality risk assessment, design of experiments can be applied to estimate the influence of CPPs [6]-[7].

4. DESIGN SPACE FOR ANALYTICAL METHODS

Definition of the DS of analytical method starts with the analysis of all available literature and scientific information. Adequate definition of DS implies the selection of significant critical process parameters (CPPs) mostly obtained from the previously conducted risk assessment. Therefore, it is possible to define analytical method as a wider range of conditions. Analytical DS is a multivariate range of the values of operating conditions whereby probable quality outputs are provided. DS is a measure of the robustness of analytical method [6]-[7].

DS assures the quality and work in DS does not represent a change. It enables higher level of flexibility in routine. Therefore, method transfer is much easier to conduct [6].

The basis for DS is the right choice of type and range of experimental factors which show the most significant influence on the chosen responses. This presents the knowledge space (KS) which has to create variations in range and intensity of the obtained responses. It is important that they satisfy the minimal requirements of CQAs.

KS is defined with the use of quality risk assessment tools, previous knowledge and preliminary experiments. Design of experiments is effective way for the evaluation of the effects of variables and their interactions. This approach also enables the modeling and prediction of the relationship between factors and CQAs or specific response. Adequate design of experiments has minimal number of experiments and satisfying statistical properties. Two types of design of experiments can be distinguished.

KS as experimental area can be investigated by screening design of experiments (fractional two-level or Plackett-Burman design). These screening designs of experiments can be replaced by preliminary conducted experiments and previous knowledge. In response-surface methodology it is possible to apply full factorial, central composite, Box-Behnken, fractional factorial, Doehlert or D-optimal design in order to evaluate the effects of the factor [6]-[7].

If experiments are performed with the application of response-surface design, the model is interpreted by mean response surface which illustrates the way of behaving of the measured response. The mean response surface does not present the guarantee that CQA would achieve defined criteria with high level of probability. This is a region of average response. Therefore, other approaches consider uncertainty between model and parameters and inform about fulfillment of the specification criteria [6].

Bayesian modeling or Monte-Carlo simulations include uncertainty of the model parameters and access the level of probability of meeting the specifications. Definition of analytical DS requires the implementation of the methodology which considers the uncertainty of the parameters of the model, the correlation of responses and the measure for the assurance of quality. Therefore, Monte-Carlo simulations provide quantitative measure of variations of modeled response [6-7].

Operative working point can be chosen based on optimum which has high index of desirability or highest level of probability for CQAs. Selection is also possible based on practice, because the only condition is inclusion of point in DS. The recommendation is to choose working point based on robustness, because the aim is to find a response plateau, not just a single function maximum. It is sometimes possible to select conditions directly from CQA diagram, because it can point to high or low robustness level [7].

5. ROBUSTNESS TESTING

Robustness testing conducted during validation process often led to results which indicated that method had to be re-optimized. AQbD concept incorporates method robustness into method qualities. It is reviewed in method optimization phase during the selection of DS and working points. DS is a region of theoretical robustness because modified conditions do not affect separation significantly. Robustness evaluation can be performed using different concepts. Design of experiments methodology with Monte-Carlo simulations can be used for successful quantitative modeling of robustness during the development of liquid chromatographic method. It is also possible to perform completely new design of experiments in the area around working point (Plackett-Burman design or two-level fractional factorial design) [7].

6. METHOD CONTROL STRATEGY

Efficient control strategy relates to planned set of controls which must ensure the consistent production of required product performances and quality. In AQbD control strategy relates to controls of input variables with the aim to assure that developed method will fulfill system suitability and performance-related requirements. System suitability test ensures method performances, prevents model failure and prevents inadequate results. Sometimes it is necessary to support system suitability test with other controls in order to manage all risks, so possible strategy could be clear precision of acceptable ranges for all critical values [7].

The method performance is definitely proved by a control strategy. It is necessary to select specific responses and to monitor them constantly, which represents the validity test (minimal, maximal or acceptable value) [6].

The basis for adequate control strategy is method development and method verification phase. Continuous monitoring of analytical method is done through monitoring of method performance with the aim to ensure that method will retain its compliance. Control charts and tools which control system suitability are widely used. Continuous monitoring identifies any out-of-trend result of developed analytical method [8].

7. EXAMPLES OF DESIGN SPACE OF ANALYTICAL METHODS

There are numerous examples of DS of methods for analytical purposes in the literature. Most of them involve liquid chromatographic methods. Measured CQAs in these methods were resolution, separation criteria, total run time, tailing factor or signal-to-noise ratio. Comprehensive literature review definitely revealed that DS can be constructed for analytical method development [6].

It is demonstrated that multiple variables significantly influence results of analytical procedure. Regulatory flexibility can be accomplished using AQbD concept, but on the other hand it is necessary to have high level of resilience, knowledge and understanding of analytical methods [10]-[15].

8. CONCLUSION

DS is a region in which critical process parameters provide assured quality. It is possible to move inside of established DS in analytical methods without the need for regulatory approval. The aim is to prove that it is possible to achieve the quality requested for CQAs with high level of probability. It is of crucial importance to establish control strategy with the aim to assure daily performance of the developed method. Appropriate control strategy is defined by methodology applied for definition of analytical DS, which must be part of quality system with risk assessment plan. This concept has significant advantages and shows wide regulatory flexibility. The conclusion is that wider DS consequently ensures more flexible and robust analytical method regarding to variations. DS ensures that the values of CQAs can be accepted in any point, which means that method robustness testing is a part of method optimization. AQbD should definitely be wider implemented in practice along with clear protocols.

9. REFERENCES

- [1] U.S. Food and Drug Administration (FDA), Department of Health and Human Services: Pharmaceutical quality for the 21st century, A risk-based approach progress report, Washington, DC, USA, 2007.
- [2] U.S. Food and Drug Administration (FDA), Department of Health and Human Services: Guidance for industry PAT – A framework for innovative pharmaceutical development, manufacturing, and quality assurance, Washington, DC, USA, 2004.
- [3] ICH topic Q8(R2): Pharmaceutical development, Fed. Regist., Geneva, Switzerland, 71(98), 2009.
- [4] ICH topic Q9: Quality risk management, Fed. Regist., Geneva, Switzerland, 71(106), 2006, 32105-32106.
- [5] ICH topic Q10: Pharmaceutical Quality System, Fed. Regist., Geneva, Switzerland, 74(66), 2009, 15990-15991.
- [6] Rozet E., Lebrun P., Debrus B., Boulanger B., Hubert, P.: *Design spaces for analytical methods*, Trends in Analytical Chemistry, 42: 157-167, 2013, <https://doi.org/10.1016/j.trac.2012.09.007>.
- [7] Orlandini S., Pinzauti S., Furlanetto S.: *Application of quality by design to the development of analytical separation methods*, Analytical and Bioanalytical Chemistry, 405(2-3): 443-50, 2013, doi: 10.1007/s00216-012-6302-2.
- [8] Peraman R., Bhadraya K., Reddy Y.P.: *Analytical quality by design: a tool for regulatory flexibility and robust analytics*, International Journal of Analytical Chemistry, 868727, 9 pages, 2015, doi: 10.1155/2015/868727.
- [9] Dispas A., Avohou H.T., Lebrun P., Hubert P., Hubert C.: *'Quality by Design' approach for the analysis of impurities in pharmaceutical drug products and drug substances*, Trends in Analytical Chemistry, 101: 24-33, 2018, <https://doi.org/10.1016/j.trac.2017.10.028>.
- [10] Bairagi A., Kothrukar R., Chikhale H., Kosanam S., Borse L.: *AQbD-novel strategy for analytical methods*, Future Journal of Pharmaceutical Sciences, 10: 138, 2024, <https://doi.org/10.1186/s43094-024-00706-1>.
- [11] Otašević B., Šljivić J., Protić P., Maljurić N., Malenović A., Zečević M.: *Comparison of AQbD and grid point search methodology in the development of micellar HPLC method for the analysis of Cilazapril and Hydrochlorothiazide dosage form stability*, Microchemical Journal, 145: 655-663, 2019, <https://doi.org/10.1016/j.microc.2018.11.033>.
- [12] Vemić A., Rakić T., Malenović A., Medenica M.: *Chaotropic salts in liquid chromatographic method development for the determination of pramipexole and its impurities following quality-by-*

- design principles*, Journal of Pharmaceutical and Biomedical Analysis, 102: 314–320, 2015, <http://dx.doi.org/10.1016/j.jpba.2014.09.031>.
- [13] Debrus B., Lebrun P., Mbinze Kindenge J., Lecomte F., Ceccato A., Caliaro G., Mavar Tayey Mbay J., Boulanger B., Marini R.D., Rozet E., Hubert Ph.: *Innovative high-performance liquid chromatography method development for the screening of 19 antimalarial drugs based on a generic approach, using design of experiments, independent component analysis and design space*, Journal of Chromatography A, 1218: 5205– 5215, 2011, doi:10.1016/j.chroma.2011.05.102.
- [14] Dispas A., Lebrun P., Andri B., Rozet E., Hubert Ph.: *Robust method optimization strategy—A useful tool for method transfer: The case of SFC*, Journal of Pharmaceutical and Biomedical Analysis, 88: 519–524, 2014, <http://dx.doi.org/10.1016/j.jpba.2013.09.030>.
- [15] Xuan D.T., Nguyen H.M.T., Hoang V.D.: *Recent applications of analytical quality-by-design methodology for chromatographic analysis: A review*, Chemometrics and Intelligent Laboratory Systems, 254, 105243, 2024, <https://doi.org/10.1016/j.chemolab.2024.105243>.