IOSR Journal Of Pharmacy www.iosrphr.org
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 8, Issue 10 Version. I (October 2018), PP. 05-10

Analytical procedures lifecycle management: An overview

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Abstract: The concept of QbD that has already given positive results, can be applied to the analytical methods as well. AQbD approach is based on ICH Q8, Pharmaceutical development; ICH Q9, Quality risk management and ICH Q10, Pharmaceutical quality system, with the same steps as in the technological process of QbD, including: definition of the analytical target profile, ATP; critical quality attributes of the methods, CQAs; risk assessment; method operable design region, MODR; control strategy and lifecycle management. By applying the design of the experiments, DoE, which is used to determine the link between the factors that influence the method's performance and the results obtained, one acquires information for the influence of more variables. The whole process of applying of AQbD should be based on solid scientific evidence. The application of AQbD shall strengthen the concept "right analytics at right time". In this approach, the robust methods are being developed, the analytical method can be applied in the framework of the defined MODR, the number of out of specification (OOS) and out of trend (OOT) results is being reduced and regulatory flexibility is enabled.

Keywords –analytical quality by design, analytical target profile, design of experiments, lifecycle management

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Date of Submission: 06-10-2018 Date of acceptance: 22-10-2018

I. INTRODUCTION

"*All analytical measurements are wrong; it's just a matter of how large the errors are, and whether they are acceptable*." Mike Thompson, Imperial College, London.

The assurance of 'fitness for purpose' of analytical procedures is a critical part of any process for ensuring drug quality. The suitability of its use is confirmed and stated by the method validation process, which can be conducted through some of the published guidelines [1-3]. The method validation is a process which confirms that the method is suitable and convenient for the forthcoming examination, i.e., it can be used for analyses of appropriate samples. The aim of the validation of the analytical method is to ensure that the results, in every following measurement, will be close enough to the unknown true value. The validation process consists of: defining the method, successive performance of the validation experiments and statistical elaboration of the obtained values in order to check the method's performance in terms of the referential, previously defined values. Certain parameters that are not included and are not evaluated during the validation of the analytical method, such as: sample's characteristics, variations of the used apparatus, the method of instrument's calibration etc., have significant influence on the results obtained by applying a validated method. Therefore, not always is there a guarantee for the robustness and other characteristics that would prove the quality of the method. The reason for that lies in the fact that the guidelines for validation of the analytical method, prepared as directions that need to be used in combination with the substantial scientific evidence, are most commonly interpreted as mandatory requirements. This might as well be the expected approach, having in mind that with their application the suitability of the method for the use is determined, through examining the defined parameters for validation (specificity, linearity, precision, accuracy), but they do not give a framework that shall provide understanding and controlling of the sources and the factors for variability of the method, and respectively, of the results [4].

By these reasons, contemporary, new proactive approach in the development and validation of the analytical method is the lifecycle management of analytical procedure. The basis of the new approach is in the guideline ICH Q8, Pharmaceutical development [5], in combination with the guidelines ICH Q9, Quality risk management [6] and ICH Q10, Pharmaceutical quality system [7]. Currently, at the very beginning of the preparation, step 2, is the guideline ICH Q12, The technical and regulatory considerations for the pharmaceutical product lifecycle management [8]. After the finalization, this guideline will undoubtedly give new dimension to the quality of the analytical method. The guideline ICH Q8 (R1) refers to ensuring the drug quality during the pharmaceutical development and manufacture, by applying the concept of Quality by Design, QbD. In ICH Q8 (R1), QbD is defined as "*systematic approach that starts with previously defined aims and emphasizes the great importance of the product and the production process, the process control, and is based on*

sustainable scientific evidence and management of the risk for quality". This practically means that the characteristics of both the product and the process performance are scientifically designed to accomplish specific goals [9]. The concept of ObD can be applied to the analytical methods as well, due to which, the critical variables of the method that should be followed and controlled could be identified by the systemathic evaluation [10,11]. This approach in developing analytical methods represents an extension of the stated guidelines, by applying the QbD approach [12-14]. In that way, the metrological approach is also included in the concept, which, on its behalf ensures that the measurement uncertainty of the results is controlled to the point when the method becomes "*suitable for the intended purpose*".

In the last few years, increased number of research papers on the application of QbD approach for development and validation of the methods for determination of active substances [15,16], impurities in the pharmaceutical dosage forms [17, 18] and stability-indicating methods [19] have been published.

II. ANALYTICAL QUALITY BY DESIGN

Analytical quality by design, AQbD, could be defined as "*collecting and evaluating data and knowledge gained within the designing of the method through its lifecycle of use, by which scientific methods are obtained that the method shall permanently give results with high quality*" [20].

AQbD approach is based on several crucial principles [20]:

- previously defined aims of the method;
- comprehension of the method, meaning explaining the performance of the method as a function of the variables;
- designing control strategy for the variables of the method in a manner which will ensure that the method will obtain data with high quality;
- evaluation of the method's performance from the start of its designing and through its lifecycle.

The application of AQbD and the lifecycle management of the analytical method is a holistic approach that results in designing more robust methods which shall provide consistent, accurate and quality results. The application of this paradigm enables the analytical method to be controlled throughout its whole lifecycle, if the goals of the methods were carefully and meticulously defined. [21].

The analytical quality by design is a complex process that includes the same steps as the technological process of quality by design which refers to ensuring the drug quality during the pharmaceutical development and manufacture: defining the analytical target profile, ATP, Critical quality attributes of the methods, CQAs, risk assessment; method operable design region, MODR; control strategy and lifecycle management. Application of QbD concept to analytical methods (AQbD) is presented on Figure 1.

Figure 1. Application of QbD concept to analytical methods (AQbD)

II.1 **Analytical target profile (ATP)**

The first step of the development of the analytical method with the AqbD approach is defining the analytical target profile, ATP, which represents the prospective overview of the aims of the analytical method, as well as defined quality requirements that the methods need to fulfill, without specifying the method [22]. The ATP design includes defining the analytes that shall be determined, the matrix in which they will be determined, the concentration region and the parameters which will be used to evaluate the performance and the quality of the method. Based on the defined ATP, activities have to be planned for selection, designing and development of the method [23]. ATP is based on understanding and interpreting the target measurement uncertainty which represents a maximum uncertainty that the obtained results should have in order to sustain the acceptable limits of confidence in their quality [24,25]. The definition of the target analytical profile is the basis of AQbD and serves as a referential model for the evaluation of the analytical method's suitability, not only in the development stage, but also when including the overall changes during its total lifecycle. It is of great importance to underline that the target analytical profile is oriented towards defining the acceptable quality of the obtained results and should not be connected to the specific analytical method or technique. It means that when ATP is designed, the stated requirements could be fulfilled by more than one method or technique. This

changes the paradigm, from placing requirements "*how*" to measure to placing requirement "*what*" to measure [26].

II.2 Method operable design region (MODR), Critical quality attributes of the methods (CQAs)

The next step in AQbD is defining Method operable design region, MODR. MODR is defined as an experimental safety zone in which the method's variables do not have significant influence on the robustness and quality of the method [27,28]. MODR represents a multivariable scientific approach based on the risk assessment which evaluates the effect of different variables on the methods' performance and the obtained results. In the current practice, the development, optimization and validation of the method are based on the principle "*one variable at a time*", which means that one variable is optimised while the rest are constant [29]. This approach always results in relatively small robustness of the method in reference to those variables examined during the method's development, and connected with the apparatus. In order to determine connection between the factors that influence on the method's performance (heating time during the extraction, temperature of the extraction, the concentration of reagents during extraction, the volume of the extraction, the type of column, flow, size of the sample) and the obtained results Design of Experiments, DoE is used. DoE provides information for the influence of more variables [30]. Different experimental designs like: Factorial Design, Central Composite Design (CCD), Box-Behnken Design (BBD) and Optimal Design (OD) are employed for prediction and optimization of analytical responses in more analytical techniques [31-33]. Those designs help in clarifying the influence of different CQAs on analytical responses.

DoE can be applied during the method's development and the obtained results can be used during the method's qualification (validation) [34]. With the evaluation of the results, data for those variables that have statistically significant influence were obtained. The comparison of these data (experimentally gained measurement uncertainty) with the previously defined total measurement uncertainty can point out that the influence of the variable is practically insignificant or practically significant. Thus, practically significant and critical variable is identified. This variable can be controlled, changed a bit or, in the worst case, the procedure should go back and start from the very beginning of the development of the analytical method.

II.3 Risk assessment

When defining MODR of the analytical method and performing of experiments assigned in DoE, the approach of risk assessment and risk management should be used. According to the definition in ICH Q9, managing the quality risk for the analytical method could be defined as a systematic process for assessment, control communication and review of the risks to the quality of the data obtained during the lifecycle of the analytical method [6]. This can be achieved by preparing the check-lists and diagrams. A useful tool for conducting the assessment activities and risk management is *cause and effect analysis*, developed in 1960 by professor Kaoru Ishikawa, who was a pioneer in the field of quality management [35]. By applying this diagram, known as Ishikawa diagram or fishbone diagram, all the potential and/or real variables are evaluated, the influence of different variables is compared, and those that have significant influence are identified. For example, in the liquid chromatographic method, the CQAs which are examined could be: the components of the mobile phase, pH of the buffer solution, the column age, the stationary phase, the
flow rate, the samples' cleanness, the wavelength and analytical responses, as: peak area, retention time, peak resolution, tailing factor, theoretical plates (Fig. 2).

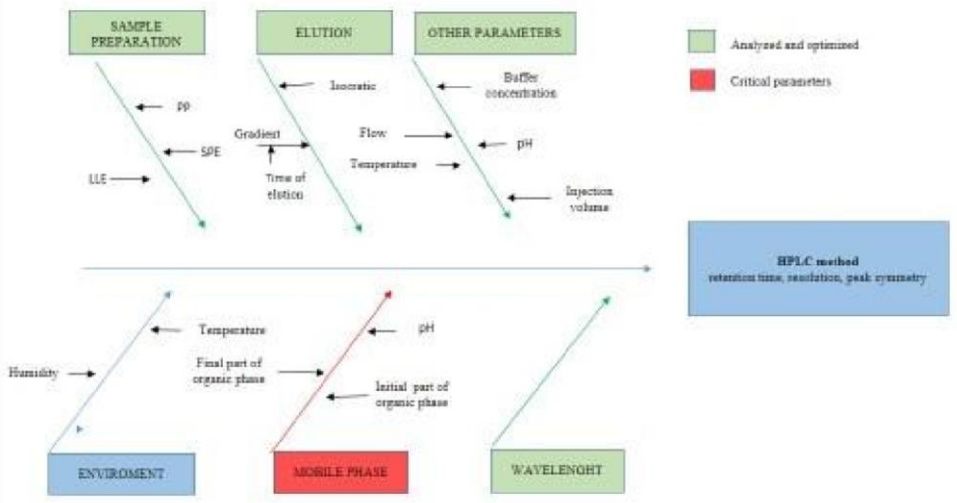

Figure 2. Ishikawa diagram for HPLC method for determination of antiepileptics in human plasma [36] *with permission*

II.4 **Control strategy**

The critical variables identified during the method's design and performance of the experiments assigned in DoE, must be properly controlled during the routine application of the method by placing a suitable control strategy [37]. The control strategy includes the critical variables with the established limits of tolerance, the way of their monitoring/control (temperature control, application of control diagrams, use of reference materials for periodical reverification experiments), frequency and documentation of the controls [38]. And so, a stronger connection between the method's application and performance and the quality of the obtained results is founded. As a final aim it is ensured that ATP is realised throughout the whole lifecycle of the analytical method. The establishment of the control strategy provides proactive approach which enables identification of the out-of-trend characteristics of the method's performance and proper reaction. In the control strategy, periodically re-evaluation of the analytical methods should be proscribed in order to introduce changes due to the improvement of the existing technology or implementation of new technologies.

II.5 **Lifecycle management and continuous improvement**

The overall approach of development, validation and monitoring of the analytical method, is, in fact, managing of the lifecycle of the analytical method. This approach provides development of robust methods, applicable during the whole lifecycle of the analytical method [38]. Managing the analytical method lifecycle means identifying, understanding, reducing and controlling the sources of variability with proactive approach which includes establishment of the robust control strategy. Main instigator of the lifecycle management of the analytical method is the establishment and understanding of the target analytical profile together with the target measurement uncertainty. Throughout the overall process, by applying the solid science it should be proved that the analytical method shall fulfill the previously defined requirements for measurement uncertainty during the whole lifecycle. It means that the analytical method is suitable for the intended use [31,39]. In addition, in the lifecycle management of the method, it is necessary to introduce continual improvement which comes out of the experience and data provided by the routine application of the method.

III. BENEFITS AND REGULATORY FLEXIBILITY

The application of AQbD results in number of benefits. With this approach: the robust methods are developed (the sources of the method's variability are understood, reduced and controlled); the analytical method can be used in the framework of the defined MODR; the number of out of specification (OOS) and out of trend (OOT) results is reduced [40]; the regulatory flexibility is enabled, meaning the changes that are in the framework of the defined MODR do not have to be identified and reported as variations [23]. The analytical method is a crucial part of the quality control strategy, which includes process controls, specifications of a finished product, analytical methods and frequency of monitoring and control. It is expected that the application of AQbD will strengthen the concept "*right analytics at right time*". The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in January, 2013 started the joint project for parallel assessment of the applications that contain elements of QbD, including AQbD. The aims of the project are: development and validation of the method (HPLC) with the application of AQbD; defining the protocols for the method's transfer; establishing methodology for verification of MODR after method's transfer; defining criteria for evaluation of the methods established by the AQbD approach. Based on the data from the report published in 2017, a more intensive work is to be expected on the field of application of AQbD, which will contribute to the development of robust methods and achievement of the expected regulatory flexibility.

IV. CONCLUSION

Quality by design, QbD is a significant part of the analytical method quality. The concept of QbD basically means that the quality can be planned and most of the problems connected with the quality derive from the way how the quality is planned in the beginning. QbD is a systematic approach for the pharmaceutical product, design and development. Although QbD approach for the analytical method (Analytical quality by Design, AQbD) is not a mandatory regulatory requirement, the literature data in the recent years are a proof of the advantages of the application of QbD in the efficient development of different analytical methods. Therefore, the paradigm of implementation of the QbD for development of the robust analytical method became necessary. AQbD does not mean less analytical experiments, on the contrary, it means right analyses in the right time, which is based on solid science and risk assessment. The QbD approach in the development of the analytical method is multi-level process.

REFERENCES

[1] ICH Harmonised guideline Q2(R1) Validation of analytical procedures: text and methodology, 2005.
[2] FDA Guidance for industry: process validation: general principles and practices, 2011.
[3] Analytical Procedures and Methods Validation for Drugs and Biologics, Guidance for Industry, 2015.
[4] E. Rozet, E. Ziemons, RD. Marini *et al.* Quality by design compliant analytical method validation, *Anal. Chem. 84*, 2012, 106-12.
[5] ICH Harmonized guideline Q8(R2) Pharmaceutical development, 2009.
[6] ICH Q9 Harmonised guideline Quality risk management, 2005.
[7] ICH Q10 Harmonised guideline Pharmaceutical quality system, 2008.
[8] ICH Q12 Harmonised guideline Technical and regulatory considerations for pharmaceutical product lifecycle management, draft version, 2017.
[9] L.X Yu, G.Amidon, M.A.Khan *et al*.,Understanding pharmaceutical quality by design, *The AAPS Journal, 16(4)*, 2014, 771-783.
[10] P. Borman, P. Nethercote, M. Chatfield *et al*., The application of quality by design to analytical methods, *Pharm. Technol*., *31 (10*), 2007, 142 – 152.
[11] A.H.Schmidt and I.Molnar, 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., 78-79*, 2013, 65-74.
[12] K.L.Barnett, P.L.McGregor, D.J.LeBlond *et al*., Stimuli to the revision process:analytical target profile;structure and application throughout analytical lifecycle, *Pharm. Forum, 42(5)*, 2013.
[13] M.Hanna-Brown, P.Borman, S.Bale *et al*.,Development of chromatographic methods using QbD principles, *Separation Sciences, 2*, 2010, 12-20.
[14] F.G.Vogt and A.S.Kord, Development of quality-by-design analytical methods, *Journal of Pharmaceutical Sciences, 100 (3)*, 2011, 797-812.
[15] J.Musters, L.van den Bos, E.Kellenbach, Applying QbD principles to develop a generic UHPLC method which facilitates continual improvement and innovation throughout the product lifecycle for a commercial API, *Organic Process Research&Development, 17(1)*, 2013, 87-96.
[16] N.V.V.S.S.Raman, Y.R.Mallu, H.R.Bapatu, Analytical quality by design approach to test method development and validation in drug substance manufacturing, *Journal of Chemistry, 2015*, 2015, 1-8.
[17] DA Bath and SI Rane, QbD approach to analytical RP-HPLC method development and its validation, *Int J Pharm Sci, 3*, 2011, 179-87.
[18] S Karmarkar, X.Yang, R.Garber *et al*., Quality by design (QbD) based development and validation of an HPLC method for amiodarone hydrochloride and its impurities in drug substance, *J Pharm Biomed Anal*., *100*, 2014, 167-174.
[19] S. Beg, G.Sharma, OP.Katare *et al*., Development and validation of a stability-indicating chromatographic method for estimating olmesartan medoxomil using quality by design, *J Chromatogr Sci*., *53*, 2015, 1048-59.
[20] P. Nethercote and J. Ermer, Quality by design for analytical methods: implications for method validation and transfer, *Pharm. Technol*., *36 (10)*, 2012, 74 – 79.
[21] GP Martin, KL Barnet, C. Burges *et al*., Lifecycle management of analytical procedures: method development, procedure performance qualification and procedure performance verification, *Pharm. Forum, 39(5)*, 2013.
[22] FG. Vogt and AS. Kord, Development of quality-by-design analytical methods, *J Pharm Sci*., *100*, 2011, 797812. [23]R. Peraman, K. Bhadraya and Y. P. Reddy, Analytical quality by design: A tool for regulatory flexibility and robust analytics, *International Journal of Analytical Chemistry, 2015*, 2015, 1-7.
[24] C.Burgees, P.Curry, DJ.LeBlond *et al*., Stimuli to the revision process: fitness for use: decision rules and target measurement uncertainty, *Pharm. Forum, 42(2)*, 2016.
[25] J.Weitzel and M.Lee, Establishment of measurement requirements-analytical target profile and decision rules, Method validation in pharmaceutical analysis: A guide to best practice, second, completely revised and updated edition, 2015, 41-58.
[26] P. Nethercote and J. Ermer, Analytical validation within the pharmaceutical lifecycle, Method validation in pharmaceutical analysis: A Guide to best practice., Second edition, Wiley-VCH Verlag GmbH & Co. KGaA., 2015.
[27] I.Molnar, H.J.Rieger, K.E.Monks, Aspects of the design space in high pressure liquid chromatography method development, *Journal of Chromatography, 1217(19)*, 2010, 3193-3200.
[28] K.E.Monks, H.J.Rieger, I.Molnar, Expanding the term design space in high performance liquid chromatography (I), *Journal of Pharmaceutical and Biomedical Analysis, 56(5)*, 2011, 874-879.

[29] S. Colgan, M. Hanna-Rrown, J. Pellet J., *et al*., Using Quality by design to develop robust chromatographic methods., *Pharm. Technol., 38 (9),* 2014, 1 – 10.
[30] T.A. Little, Design of experiments for analytical method development and validation, *BioPharm International, 27 (3),* 2014, 1 – 3.
[31] S. Beg, V. Chaudhary, G. Sharma,B. Garg*et al*., QbD-oriented development and validation of a bioanalytical method for nevirapine with enhanced liquid-liquid extraction and chromatographic separation. *Biomed Chromatogr., 30*, 2016, 818-828.
[32] L.Taevernier, E. Wynendaele, M. D'Hondt *et al.,* Analytical quality-by-design approach for sample treatment BSA-containing solutions, *J of Pharm. Analysis, 5(1),* 2015, 278-32.
[33] GR. Deshpande, AK.Roy, NS.Rao *et al*., Rapid screening of volatile ion-pair reagents using UHPLC and robust analytical method development using DoE for an acetyl cholinesterase inhibitor: galantamine HBr. *Chromatographia 73(7), 2011,* 639-648.
[34] P.Shah, J.Patel, T.Gandhi, Development and validation of HPTLC method for the simultaneous estimation of clonazepam and paroxetine hydrochloride using a DOE approach,*J Taibah Uni Sci., 11*, 2017, 121-32
[35] K. Ishikawa, (Lu. D. J. trans.), *What is Total Quality Control? (*Prentice-Hall Inc., Englewood Cliffs, NJ, 1985).
[36] A.H.Zajmi, *Bioanalytical methods for determination of new generation antiepileptic drugs*, doctoral diss., Faculty of Pharmacy, Ss Cyril and Methodius University, Skopje, 2017.
[37] E. Rozet, L. Pierre, M. Jean-Francois *et al*., Analytical procedure validation and the quality by design paradigm, *J Biopharm Stat*., *25(2),* 2015, 260-8.
[38] J.deSousa, D.Holt, P.A.Butterworth, Analytical method design, development and lifecycle management, Wakiria S.Schlindwein, Mark Gibson (ED.), *Pharmaceutical quality by design, A Practical approach*, (Wiley Online Library, 2018), Chapter 10.
[39] M.S.Hasnain, S. Siddiqui, S. Rao *et al*., QbD-driven development and validation of a bioanalytical LC-MS method for quantification of fluoxetine in human plasma., *J Chrom Sci*., *54*, 2016, 736- 743.
[40] L.D.Torbeck, OOS, OOT, OOC and OOSC, *Pharmaceutical Technology, 35 (10),* 2011, 46-47.

Ljupka Koteska. "Analytical procedures lifecycle management: An overview." IOSR Journal of Pharmacy (IOSRPHR), vol. 8, no. 10, 2018, pp. 05-10.