INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

IMPLEMENTING OF ANALYTICAL QUALITY BY DESIGN FOR HIGH QUALITY PHARMACEUTICAL PRODUCTS

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ARTICLE INFO

Article history
Received 30/06/2017
Available online
30/07/2017

Keywords
Quality by design,
PAT (Process analytical techniques),
AQbD (analytical quality by design),
MODR (method operable design region),
ATP (Analytical Target Profile),
DOE (Design of Experiments),
CMM (Continous Method Monitring).

ABSTRACT

The quality in the pharmaceutical industry has become a very important topic. Pharmaceutical industry has been emerging rapidly for the last decade by focusing on product Quality, Safety, and Efficacy. The guidelines of ICH from Q8 to Q11 have discussed QbD implementation in pharmaceutical product formulation development. ICH Q11 is a clear discussion about QbD approach for API (Active Pharmaceutical Ingredient) synthesis with examples. Pharmaceutical firms increased the number of product development by using different scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). The main key tools of AQbD are identification of ATP (Analytical Target Profile), CQA (Critical Quality Attributes) with risk assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy, AQbD Method Validation, and Continuous Method Monitoring (CMM), TQM (Total Quality Management), DOE (Design of Experiments). Implementation of AQbD simultaneously in analytical development will improve the ability of production of high quality products which will minimize the risks during every step of manufacturing and analysis of products.

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*Please cite this article in press as **P. Abhinandana** et al. Implementing of Analytical Quality by Design for High Quality Pharmaceutical Products. Indo American Journal of Pharmaceutical Research.2017:7(07).*

INTRODUCTION [1-3]

Nowadays analytical quality by design became a big concern for pharmaceutical industries as the quality should incorporate and tested in each and every step of production of pharmaceutical production. All the regulatory authorities are particular about implementing ICH Q8 to Q11 which are the guidelines regarding to Quality. So that all pharmaceutical industries has been focusing on product Quality, Safety and Efficacy. The product quality has been increasing by implementing QBD (Quality by design) and PAT (Process analytical techniques).

WHAT IS ANALYTICAL QUALITY BY DESIGN? [4-9]

Quality by design (QbD) can be defined as "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" as per ICH.[4]

AQbD is also an element which will help in maintaining product quality. By incorporating some tools related to AQbD the robustness of a pharmaceutical product can be increased. Those tools includes ATP (Analytical Target Profile), CQA, Risk Assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy and Risk Assessment. Although there is no specific discussion about this AQbD in ICH like QbD (Q11) for the better production of high quality product the scientific approach for the AQbD has become big source. Both QbD and AQbD can be applied to the product in similar time.FIG [5-9].

Figure.1.AQbD TOOLS.

THE MAJOR DIFFERENCES BETWEEN QbD AND AQbD:[10-13]

It is like traditional and scientific approach. For traditional approach there is no use of statistical calculations and risk assessments where AQbD main concept is applying of statistical calculations and risk assessments, control strategy and continuous method monitoring while preparation of pharmaceutical product and as well as development of analytical method for that product. [10-11]There is lot of benefits applying this AQbD pharmaceutically which hopefully leads to building of more quality into a product.FIG.2[12-13]

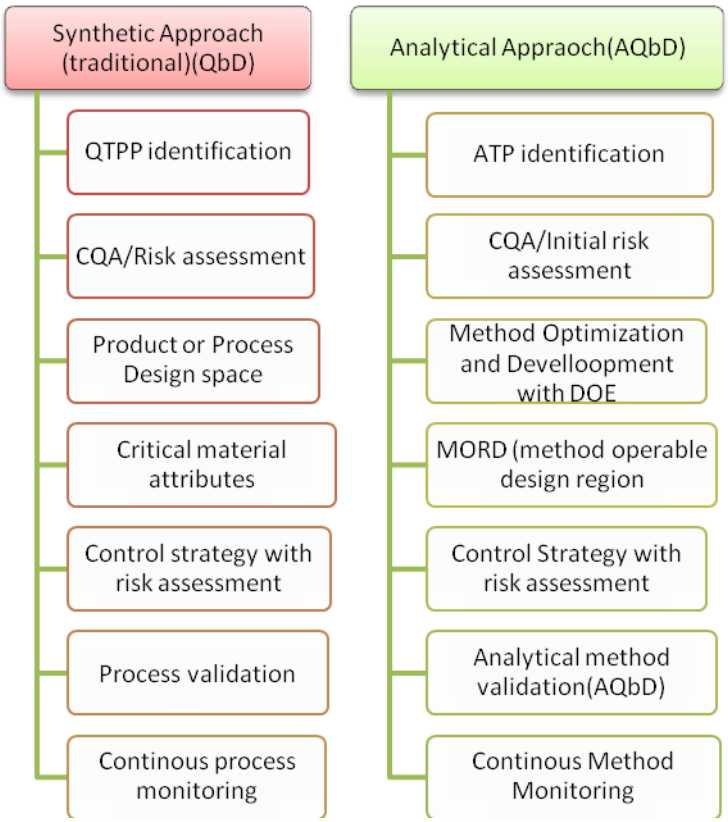


Figure.2.Tools for both synthetic and analytical development.

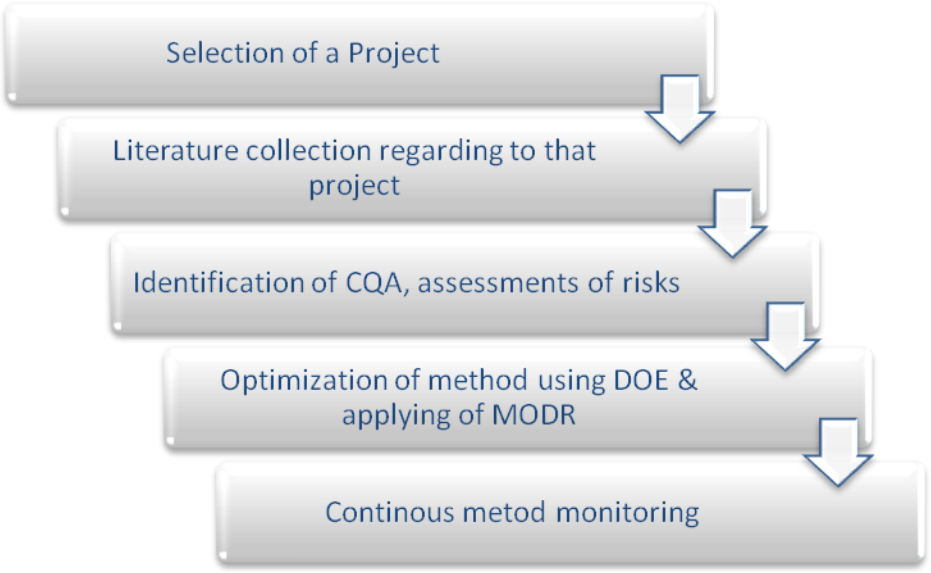
ANALYTICAL TARGET PROFILE (ATP):[14-17]

ATP is like QTTP in QbD. This will include with method selection for a particular product and all the risk assessment along with method. [14-16]

The major things that will come under ATP are

i) Type of product (whether is API or Impurity)
ii) Type of technique selection (by HPLC, GC, HPTLC or other techniques for its estimation.
iii) Method selection and its requirements (assay and impurity identification)
iv) Requirements for the procedure (solvents, solutions, columns).

ANALYTICAL APPROACH IN R&D DEVELOPMEMNT



FIR.3. AQbD Approach for an analytical method development.

ATP also involves in the selection of an analytical technique and the parameters of method requirements.

i) By FTIR or spectrophotometer
ii) HPLC or spectroscopy
iii) Assay or impurity profiling by HPLC with different detectors
iv) Impurity profiling by GC
v) Selection of method requirements like solvents needed and columns for the particular method, flow rate, wavelength, and mobile phase combinations which will comes under CQA.

CRITICAL QUALITY ATTRIBUTES (CQA):

Critical quality attribute is the parameter which involves in the selection of method requirements which includes [17]

For HPLC

(i) What is the mobile phase & its organic combinational ratios
(ii) What is flow rate and wavelength?
(iii) Diluents and drug concentration
(iv) Selection of column which suits for the drug and mobile phase

For HPTLC and TLC

(i) pH of the mobile phase
(ii) polarity
(iii) Type of TLC plate
(iv) Injection volume and its concentration
(v) Development of TLC plate
(vi) Color of the Reagents

For GC

(i) Type of carrier gas
(ii) Detector and its wavelength
(iii) Diluents and sample concentrations
(iv) Pressure of the system

All these parameters can be planned in detailed when its come to design of experiments.

INITIAL RISK ASSESSMENT [18]

Initial risk assessments come under CQA and it involves in the risk assessment and method monitoring of a particular method at early stages of process beginning. The main goal of AQbD is to develop a method which will lead to production of high quality product. This will happen only when the production or analysis of a product is monitored in each and every step and assessment of risks and plan of work which will overcome those risks.

So that risk assessment from early stages of starting material to final product is an important task.

DESIGN OF EXPERIMENTS (DOE) - [INVOLVES IN METHOD OPTIMIZATION AND METHOD DEVELOPMENT]

After the assessment of risks there is a need of design of experiments depending upon the priority of the method requirements. For an analytical method is there is necessity of proper planning of the work staring with mobile phase and ending calculation of impuritites or assay values.FIG.4 [19]

By designing in this way it is predictable what will be the result is and there is a lot of possibilities to increase the successful estimation of a product and minimization of errors. It also gives a benefit of decreasing of the repeated steps and statistical calculations are very important for evaluation of critical method variables. There is possibility to obtain good robustness within methods by DOE.[19]

METHOD OPERABLE DESIGN REGION (MODR)[20]

MODR is the tool which will provide multidimensional combinations and interactions of method parameters leading to meet measurement requirements. It will target to develop a method which is less risk to the method performance.

CONTROL STRATEGY AND RISK ASSESSMENT[21-24]

A control strategy is designed to ensure that a product of required quality will be produced consistently. For a given product various approaches for control strategy can be possible like in-process testing and end product testing.

Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimize the need for testing of end product.

The risk assessment activities indicate that the overall understanding of method performance can be improved, and the risk to obtaining reliable data is high and difficult to manage, a more appropriate method may be needed.FIG.5.

FIG.4. Method parameters for Designing of DOE for HPLC

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The risk assessment activities indicate that the overall understanding of method performance can be improved, and the risk to obtaining reliable data is high and difficult to manage, a more appropriate method may be needed.**FIG.5**. If the risks are measured low then the control strategy can be explained as defined system suitability and method can deliver the desirable method attributes. The appropriate system suitability is the controllable element which will be needed in ensuring of performance of selected method.

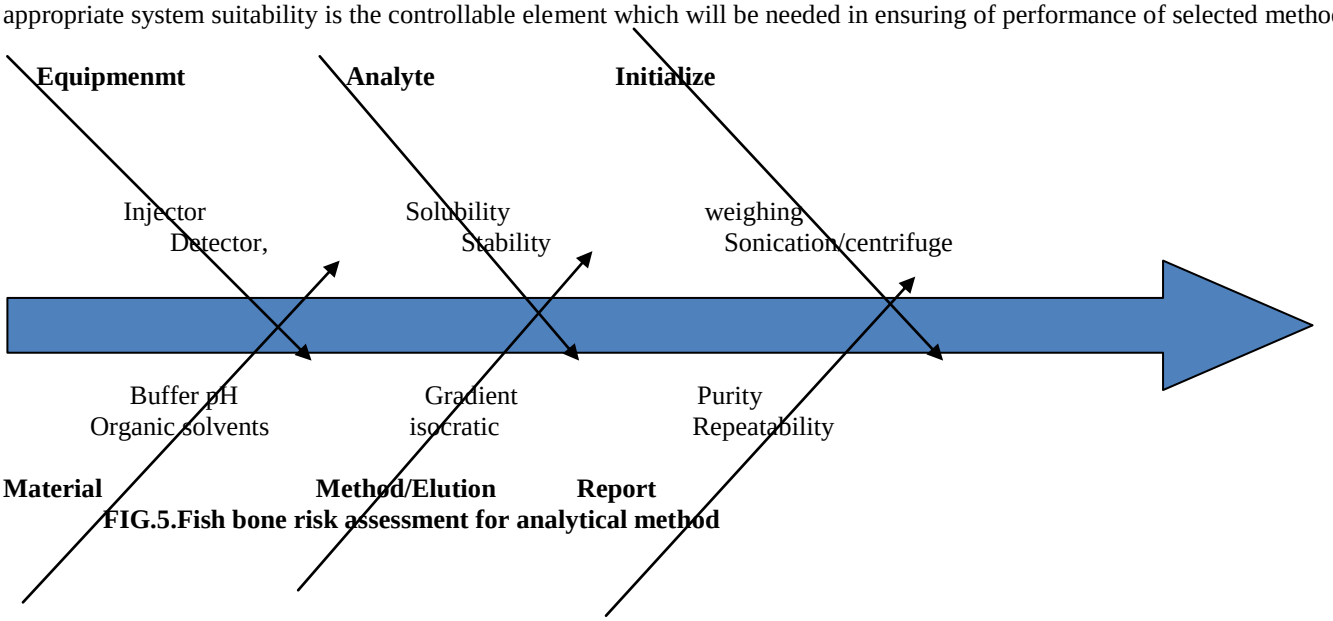

FIG.5.Fish bone risk assessment for analytical method

AQbD METHOD VALIDATION:[25-26]

Analytical quality by design Validation is required for each batch of API or final finished product for the confirmation of its quality. It will use both the knowledge from MODR and DOE for all kind of products with revalidation capability. AQbD is the tool which will reveal the product quality without any compromises by following ICH guidelines and by utilizing of control strategy and continuous improvement.

CONTINOUS METHOD MONITORING AND CONTINUAL IMPROVEMENT: [27-30]

For AQbD, CMM is the final step as it includes continual improvement of method or process throughout the product lifecycle by control strategy and risk assessments. Knowledge of design of experiments and MODR, ATP CAQ and control strategy are the tools which can monitor the product quality throughout the process and minimizing the errors in process is the main theme of these tools.FIG.6.

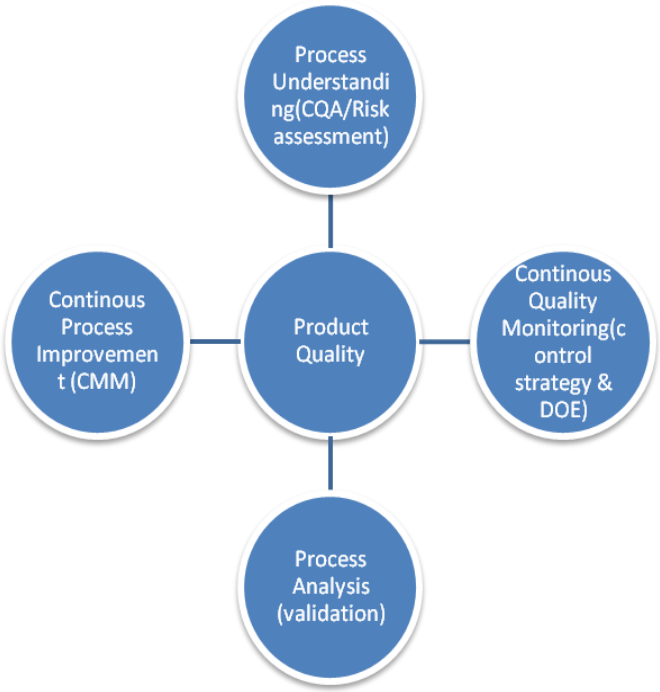

FIG.6.Product Quality monitoring.

ADVANTAGES:[31-32]

AQbD can be applied to biopharmaceutical, clinical and genetically. To deliver a product at its maximum rate of purity, potency and biological availability undoubtedly AQbD is a big hope for the pharmaceutical industries. As per ICH guidelines Q8 (Quality of pharmaceutical product) a drug product should be manufactured with proper planning and monitoring and should contain high quality at its maximum rate of availability biologically. By applying risk assessments and control strategy with continuous method monitoring as the tools of AQbD it is possible to minimize the errors in production and it will control the method failures also.

CONCLUSION

As the product quality is the main theme for the pharmaceutical industries it is preferable to apply Analytical Quality by design as the tools of this AQbD like ATP, CQA, Method Optimization and Development with DOE, MODR, and Control Strategy with Risk Assessment, Method validation and Continuous Method Monitoring (CMM), and continuous improvement will give the best results than traditional methods. Risk assessment is the main tool which is helpful to minimize the timelines and fewer chances of method failures.

REFERENCES

1. ICH. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline Q8 (R2) Pharmaceutical Development. 2009. Aug, [Last cited on 2009 Aug 30]. Available from :http://www.ich.org/ file admin/Public Web_Site/ICH_Products/ Guidelines/ Quality/ Q8_R1/ Step4/ Q8_R2_ Guideline. pdf
2. "ICH Q8 Quality guidance: Pharmaceutical Development".
3. "ICH Q9 Quality guidance: Quality Risk Management".
4. "ICH Q10 Quality guidance: Pharmaceutical Quality System"
5. M. Schweitzer, M. Pohl, M. Hanna-Brown et al., "Implications Andv opportunities of applying QbD principles to analytical measurements," *Pharmaceutical Technology*, vol. 34, no. 2, p. 52, 2010.
6. Peri P. Quality by Design (QbD) Approaches for Orally Inhaled and Nasal Drug Products (OINDPs) in the USA. [Last cited on 2009 Aug 10]. Available from: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm103526.pdf .
7. [Lionberger RA, Lee SL, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs. AAPS J. 2008; 10: 268–76. [PMC free article] [PubMed]
8. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008; 25:781–91. [PubMed]
9. Gupta A, Fuloria NK. Short review on Quality by design: A new Era of Pharmaceutical drug development. Int. J. Drug Dev. & Res. 2012; 4:19-26.
10. http://www.sepscience.com/Sectors/Pharma/Articles/559-/ The-Development-Phase-of-an-LC-Method-Using-QbD-Principles.
11. L. K. Garg, V. S. Reddy, S. S. Sait, T. Krishnamurthy, S. J. Vali, and A. M. Reddy, "Quality by design: design of experiments approach prior to the validation of a stability-indicating HPLC method for Montelukast," *Chromatographia*, vol. 76, no. 23-24, pp. 1697–1706, 2013.
12. https://www.slideshare.net/shettyuc/qbd-for-beginners-control-strategy

13. http://onlinelibrary.wiley.com/doi/10.1002/jps.22325/full
14. http://www.hplc.hu/PDFs/ZirChrom RP Guide.pdf.
15. https://www.hindawi.com/journals/jchem/2015/435129/
16. R. D. Snee, "QbD in test method development and validation," *Pharmaceutical Processing*, May 2014.
17. P. Borman, M. Nethercote, D. T. Chatfield, and K. Truman, "Application of quality by design to analytical methods," *Pharmaceutical Technology*, vol. 31, pp. 142–152, 2007.
18. M. Schweitzer, M. Pohl, M. Hanna-Brown et al., "Implications and opportunities of applying QbD principles to analytical measurements," *Pharmaceutical Technology*, vol. 34, no. 2, pp. 52–59, 2010.
19. https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=7&cad=rja&uact=8 &ved=0ahUKEwjj2or5o9PUAhXIvo8KHSfsDwUQFghcMAY&url=http%3A%2F%2Fwww.ema.europa.eu%2Fdocs%2Fen_GB %2Fdocument_library%2FPresentation%2F2009%2F11%2FWC500008742.pdf&usg=AFQjCNG1BqRi5o7YoxBPPXtW6xpVca yN2Q
20. http://www.americanpharmaceuticalreview.com/Featured-Articles/144191-Analytical-Quality-by-Design-AQbD-in-Pharmaceutical-Development/
21. http://www.sciencedirect.com/science/article/pii/S1878535214000288
22. International Conference on Harmonization of Technical Requirements for Registration of
23. .Pharmaceuticals for Human Use_Quality_IWG_PtCR2_6dec2011.6-7.
24. J. Piriou, B. Elissondo, M. Hertschuh, and R. Ollivier, "Control Strategy as the keystone of the product life cycle, from product/ process understanding to continuous process verification and improvement," *Pharmaceutical Engineering*, vol. 32, no. 1, pp. 1–8, 2012.
25. http://aktehom.com/wp-content/uploads/files/AKTEHOM avis expert 201202 ISPE control strategy.pdf.
26. http://www.ich.org/fileadmin/Public Web Site/Training/GCG - Endorsed Training Events/APEC LSIF JCCT workshop Beijing China Dec 08/Day 2/Control Strategy Case Studies. pdf.
27. https://www.hindawi.com/journals/ijac/2015/868727/
28. http://www.americanpharmaceuticalreview.com/Featured-Articles/144191-Analytical-Quality-by-Design-AQbD-in-Pharmaceutical-Development/
29. http://pubs.acs.org/doi/abs/10.1021/ac202664s
30. http://onlinelibrary.wiley.com/doi/10.1002/bit.260270719/pdf
31. https://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/lifecycle_pdf.pdf
32. https://books.google.co.in/books?id=yRAjTMwbaGYC&pg=PA375&lpg=PA375&dq=about+continuous+method+monitoring+for+hplc+methods&source=bl&ots=GuWHm7yEx0&sig=ho07sNBn1fvrxjEvLU_CZ80kyHc&hl=en&sa=X&ved=0ahUKEwjvLu4ydPUAhXMtY8KHX59AJQQ6AEIXTAH#v=onepage&q=about%20continuous%20method%20monitoring%20for%20hplc%20methods&f=false
33. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4332986/
34. https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=33&cad=rja&uact=8&ved=0ahUKEwir4LzHytPUAhXJNY8KHWiAtc4HhAWCCowAg&url=http%3A%2F%2Faustinpublishinggroup.com%2Fanalytical-pharmaceutical chemistry%2Fdownload.php%3Ffile%3Dfulltext%2Fajapc-v4id1078.pdf&usg=AFQjCNF0gcJ9idk_iqehVLQRudpJYdRCkg