RESEARCH ARTICLE

Development, Comparison, and Evaluation of Regulatory Models for Quality by Design Based On ICH Guidelines and Indian Guidelines along with Recommendations

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ABSTRACT

Quality by Design (QbD) is a flexible approach that helps to build up the quality of a product. Generally, the quality guidelines of International Council for Harmonisation (ICH) are considered for the quality by design (QbD). The ICH Q8 guidelines "Pharmaceutical Development", ICH Q9 guidelines "Quality Risk Management", ICH Q10 "Pharmaceutical Quality System", ICH Q11 "Manufacturing of drug substances" are generally followed to perform a successful QbD. Here we proposed the probable models for QbD according to the ICH guidelines and Indian guidelines and evaluated them along with a comparison study to find out the probable elements for QbD from Indian guidelines. Besides this, the work also finds out the deficiencies of considered Indian guidelines and suggests probable recommendations to improve the guidelines to develop the QbD guidelines as per Indian aspects.

Keywords: Evaluate, Guidelines, ICH, QbD, Quality, Recommendations.

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INTRODUCTION

Quality is an important aspect of the products and got more priority for pharmaceutical products as it directly deals with human beings.[1] Quality is defined as "the suitability of either a drug substance or drug product for the intended use. This term includes such attributes as the identity, strength, and purity".[2] For decades, the pharmaceutical industries are dedicated to manufacturing the quality drugs product which meets the patient requirement.[3] But despite the adoption of the GMP approach, there are still incidents of product recalls, rejections, and batches' failures as they are not meeting their quality and manufacturing standard up to the mark.[4] Ultimately, the products are failed to satisfy the customers. Hence the basic principles of customer satisfaction are not being achieved.[5] Therefore, to ensure the quality in the manufacturing process and manufacturing of standard products, a holistic and flexible approach was introduced to increase the quality of the product and to introduce the standard process for manufacturing the product with zero defect in the pharmaceutical industry which is termed as QbD.[6]

Pharmaceutical QbD is a systematic approach that deals with the objective, which is predefined and focuses on understanding process and product and process control depending upon sound sciences and quality risk management.[7,8] Through this advanced approach, we can achieve the goals like the meaningful quality specification of a product, enhancement of process as well as manufacturing capability along with the reduction in the variability of the process, increasing in the detection of root cause analysis which facilitates the post-approval change management.[9] The QbD also has several advantages like an assurance of quality, flexibility in operation, clear planning of work with team approach as well as testing balance with the design will also be ensured. Some elements of QbD, including CQA risk management (CMA), critical quality attributes (CQA), quality target product profile (QTPP), critical process parameters CPP, control strategy in each step, along with process capability and continual improvement, is applied in the industry, which plays a vital role in the development of a good quality product.[10] Generally, a modeling system is used in the quality management system. It helps a lot to understand the basic principle and elements of a subject.[11] The modeling system in a QbD will also help understand the several parameters and the basic elements in the QbD.[12] As ICH guidelines are accepted worldwide so it can be taken as standard guidelines.[13] So, by taking ICH guidelines as a standard the elements and parameters of QbD, can be used to form the modelling system for the comparison purpose with other guidelines for finding the QbD elements in other

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regulatory guidelines. So, in this work, we have tried to find the probable key elements and parameters from Indian guidelines, i.e., Drugs and Cosmetics Acts and rules 1945 and describe the gap and the probable suggestions needed to develop the guidelines for QbD.

Regulatory Aspects of Quality by Design (QbD)

Quality by Design also follows the regulatory guidelines to meet the specifications. The International Council of Harmonization establishes the regulatory guidelines that describe the several parameters and processes of QbD. The guidelines are mentioned under quality guidelines which contain four segments. Basically, ICH Q8(R2)- pharmaceutical development, ICH Q9-quality risk management, ICH Q10-Pharmaceutical Quality System, ICH Q11- development and manufacture of drug substances are followed to perform the QbD.[14]

Development of the Regulatory Models

The regulatory models were developed for QbD from both the ICH and Indian guidelines through considering the key parameters and elements. Along with this a comparison was also made to find the gaps. At last the recommendations were given for the development of guidelines.

Development of the Regulatory Models for QbD from ICH Guidelines

The description of the QbD is given in the quality guidelines of ICH, so it is considered as the standard guidelines for this work that including the guidelines Q8 (Pharmaceutical development), Q9 (Quality risk management), Q10 (Pharmaceutical quality system), Q11 (Development and manufacture of drug substances).[15] So, these guidelines are thoroughly studied for choosing the key elements of the QbD to develop the regulatory model.

Regulatory Models for ICH Q8 (R2) Guideline

The pharmaceutical development guidelines are classified into two parts in ICH Harmonized Tripartite Guidelines, where part I describes the basics of pharmaceutical development, which is further classified into three categories: an introduction of pharmaceutical development of a drug product along with its component along with a glossary. Under part II there is annex to pharmaceutical development, which consists of introduction, elements of pharmaceutical development, submission of pharmaceutical development and related information in common technical document (CTD) format, glossary. This guideline describes the several parameters of pharmaceutical development QbD like QTPP, CQA, and CMA, CPP, control strategy, design space. Besides these things, the guideline also describes the flexible regulatory approach.[16]

The model of pharmaceutical development is generally prepared by choosing the basic three elements in the guidelines. The model consists of four elements, i.e., flexible regulatory approaches, research elements, design space, and control strategy. Among these four elements, the sub-models are prepared for the first three elements, after developing all three sub-models based on that the whole models for the Pharmaceutical development were prepared. The regulatory model developed for the pharmaceutical development was connected to all the possible parameters needed to describe the QbD as a standard process.

Flexible Regulatory Approach Model

The model for a flexible regulatory approach developed through four parameters, i.e., risk-based regulatory decision, manufacturing process development by considering the design space, real-time quality control, reduction of post-approval submission (Figure 1).[16]

Evaluation

This sub-model is made by taking the four elements of four ICH Q8 guidelines which is directly related to the main element flexible regulatory approach. The quaternary modeling system is introduced to link these four elements, which connects and established the relationship of four elements with a flexible regulatory approach. The flexible regulatory approach helps in the total pharmaceutical development of an industry. It allows the design space within the manufacturing process, which helps the person to decide on the risk management system that contains continuous review and inspection of a process along with regulatory compliances. The simple regulatory system always has an approach towards design space that allows a healthy manufacturing process improvement along with a quick real-time quality control system which results in the reduction of release testing at the endpoint. The whole procedure ultimately results to prevent the post-approval submission of a product.

Research Elements Model

Research elements models also contain four elements which are CQA, CMA, design space, and QTPP (Figure 2).[16]

Evaluation

The research element model depends on the above four elements, which play a vital role in the development of QbD in the pharmaceutical industry. The CQA denote the physical, chemical, biological, or microbiological attributes of a product within a flexible limit or range. In general, for a dosage form the critical quality attributes ensure several aspects that can affect purity, stability, drug release, strength, sterility, adhesion. CQA is also related to risk management. To control the parameters of CQA, the rank of risk should be noted. During the planning of the development of a product or process in every step, the

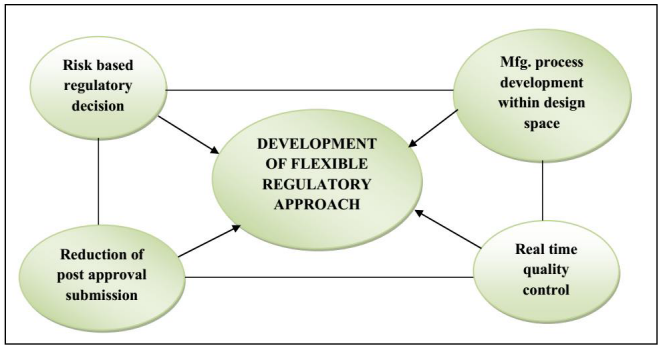

Figure: 1 Submodel for development of flexible regulatory approach

range of risk should be determined. The risk estimation should be based on the design space proposed during the development of the whole system. Based on the design space the rank of risk should be determined. The proposed design space must give a flexible approach during the development process. To give the strength of all parameters, the QTTP plays a major role. It states the quality criteria of a drug product with the suitability of marketing principles, the delivery system including the route of delivery, the pharmacokinetics data, strength of a drug, and the container closer system. So, the details CQA should be known from the QTTP and with the basic understanding of process and product design. To increase the potentiality of CQA quality risk management should be prioritized, and the flexibility of design space is linked with the risk management tool. Hence, four parameters are related to each other and are directly connected to the research parameters of QbD.

Design Space Model

Design space describes the flexibility range of a process or product. It consists of six parameters which are description of design space, unit operation design space, selection of variables, design space and the edge of failure, design space vs. existing range, relation of design space and equipment.[16] These six parameters are considering during the selection of the design space of a process or product. As the six parameters are directly related to the design space, so here we proposed a hexagonal modeling system to frame the design space where these six parameters are directly related to the design space (Figure 3).

Evaluation

The first parameter of the design spaces is its brief description. The proposed design space of a product or process must be justified. The historical data of that product or procedure may help in it. By taking into consideration of the critical material attributes and critical quality attributes along with variables, the design space should be described. For the unit operation, the design space should be created. As the design space approaches for flexibility, for one-unit operation, different design spaces can be created, or for different unit operations, the same design space can be created, which can provide more flexibility to the total operation. The selection of variables is beneficial for the design space because the risk range can be determined through the critical quality attributes and critical material attributes. By creating the design space, the edge failure can also be determined because the proposed design space shows how much it closer to the edge of risk by gaining the knowledge of material attributes. So, edge failure can be avoided by developing a healthy design space. The proposed design space must give more flexibility to the process or product than the proven existing range. During developing a design space, the flexibility of the equipment should be mentioned. Design space can be developed at any stage during scale-up. For the pilot plan operation, the risk of design space should be mentioned. So, for achieving the quality up to the mark for producing a zero-defect product, these six elements of design space play a crucial role.

Pharmaceutical Development Model

By considering the above three models and one extra element, i.e., control strategy, the final model for pharmaceutical development was prepared (Figure 4).

Evaluation

For pharmaceutical development, we proposed a pentagonal modeling system where the pharmaceutical development depends on its four fundamental pillars. Pharmaceutical development depending on the several features which are summarized in the sub-models. For the improvement of the quality of a particular product, all the elements play a vital role. The research elements describe the quality target product profile, which is related to the critical quality attributes that also helps to determine the risk range and give the flexibility of industry to design a product and process through the application of design space. Design space further contributes to the pharmaceutical development through the

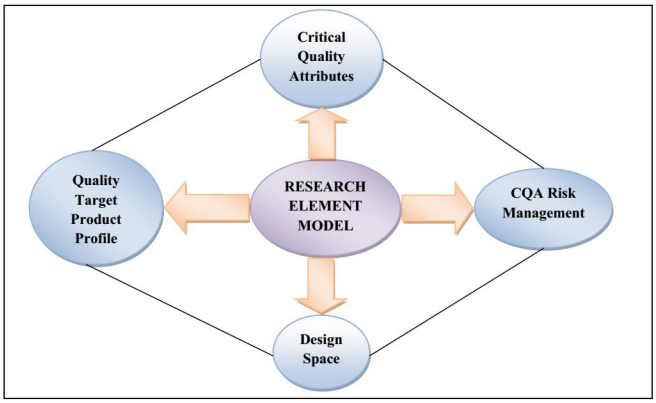

Figure 2: Submodel for Research Element

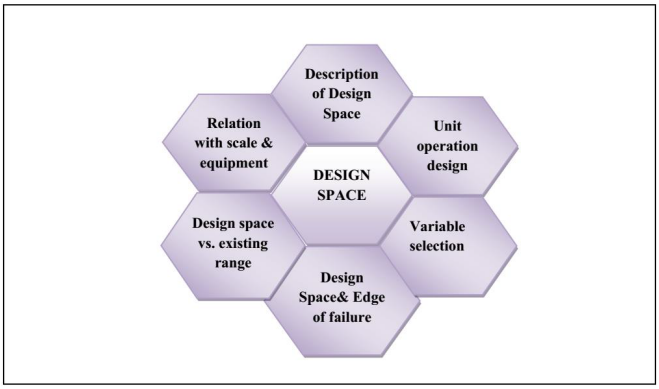

Figure 3: Submodel for design space

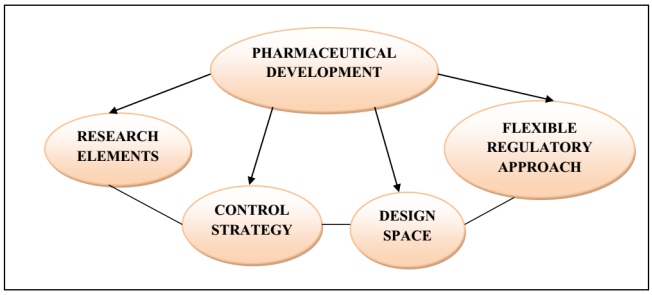

Figure 4: Pharmaceutical development model

variable selection, prevention of edge failure, justification of the range of flexibility, flexibility in several unit operations, and development of new flexible range along with designing a product in any scale. Control strategy justifies the final quality of a product or process. It is also related to critical quality attributes, critical material attributes. The operations performed in the control strategy control the input materials depending upon the further process, specification of the drug products, controls in each step of the process, in-process and endpoint testing of a product, and overall management of the total operation. All elements will work successfully when there is a flexible regulatory approach in the whole system, which helps in the continuous manufacturing of a product smoothly, real-time quality control, risk-based decision-making in each step, and above all, prevent the post-approval submission of a product. So, through this basic element and a well-developed process, the pharmaceutical development model helps to contribute to producing a quality product.

Regulatory Model for ICH Q9 Guidelines

ICH Q9 guidelines describe QRM. This guideline contains total eight points along with two annexes. The eight points describe the following things, i.e., introduction, scope, principles of quality risk management, general quality risk management process, risk management methodology, integration of quality risk management into the industry and regulatory operations, along with definitions and references. The ANNEX-I describes the risk management methods and tools and ANNEX-II focuses on the potential application of quality risk management.[17] For the product safety, efficacy, and good therapeutic value, the reduction of risk of a process and product is necessary. By taking the elements of the risk management system we proposed a T2 reverse modeling system. For initiating a risk management process, four events are generally performed: assessment, control, result, and review (Figure 5). During performing this, some sub-events are performed: identification, analysis, evaluation, reduction, and control. In the risk management system, the ranking of risk is also important. Also, the proper justification and the effect of risk to the process as well as in the products are given. Critical quality attributes of a product also play a key role in the risk management procedure. So, after evaluating all aspects of a product or process the risk management system will establish.

Evaluation

The initiation of a quality risk management process is clearly described through the above model. The first step of the quality risk management system is the assessment of the risk, which contains three steps i.e., identification of the risk, analysis of the risk, and evaluation of the risk. Assessment of the risk is also based on three fundamental points: identifying the wrong, the probability of wrong, and its consequences. Risk identification denotes the problem description through systemic information based on the previous historical data, some theoretical analysis, and feedback from the stakeholders. The second step of the assessment is the analysis of the risk. During analysis at first, the hazards are estimated. The analysis may be quantitative or qualitative, which reflects the severity of harm. In some cases, the harm was also detected. Following these two steps, the evaluation is performed, which compares the analysis and identified risk with the established risk factors. Alternatively, the risk ranking can be done during the qualitative process which can be classified by high, medium and low. The second step of the risk management system is risk control where the acceptance range of the risk is described. If the rate of risk is beyond the range then the control programmed is performed and reduction of risk is generally done to achieve the meaningful quality. During the risk control process industry considers some approaches like the acceptance level of the risk, elimination procedure of the risk, balance between benefits, risk, and resources, control of introduced risk. Following these steps, the total outcome is noted, and a review of the whole procedure was done. If the satisfactory outcome is generated by following these events then the established new quality risk is done but if it needs major changes, the whole procedure is repeated for the healthy outcome. In industry, the flexible regulatory approach plays a major role in risk communication and risk management program like regulatory approaches in process, management

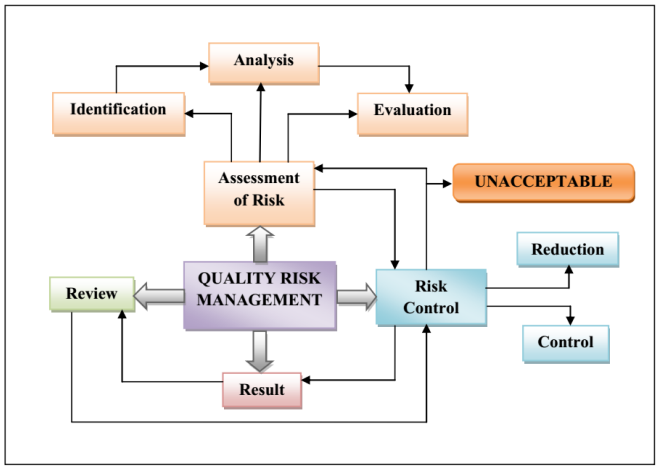

Figure 5: Quality risk management model

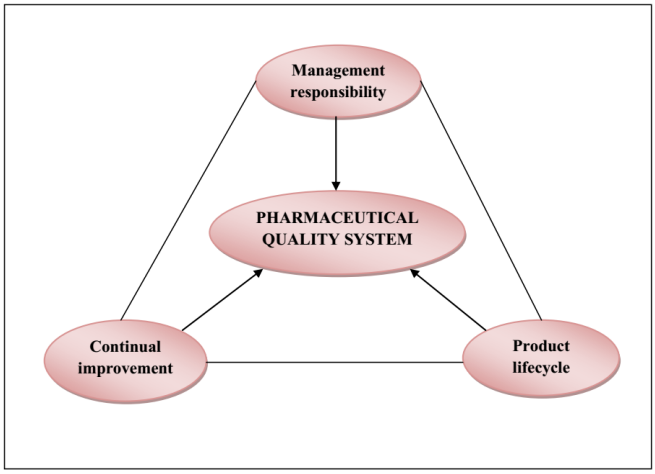

Figure 6: Pharmaceutical quality system model

system, manufacturing, and laboratory control and equipment facilities.

Regulatory Model for ICH Q10 Guidelines

ICH Q10 guidelines describe the pharmaceutical quality system (Figure 6). Here we proposed a triangular model for the pharmaceutical quality system. By taking the consideration of three major parameters, the model is formed. The pharmaceutical quality system depends on management responsibility, product lifecycle, and continual improvement.[18] These three parameters help in the total quality management (TQM) of a process and a product that leads to the overall quality management system, which ultimately helps produce the quality product and ensures the potency, therapeutic efficacy, and the product that leads to the customer satisfaction.

Evaluation

The three parameters are directly connected to the pharmaceutical quality system, which plays a major role in developing the quality product. The management responsibility is the key parameter of this model, which controls the rest of the two parameters. The responsibility of the management should be towards the dedication and commitment to the improvement of the quality management system (QMS) through the other parameters. Management must participate in the design implementation monitoring and maintenance of the pharmaceutical quality system throughout the whole life cycle of the product and advocate continual improvement. The description of individual personnel roles in the period of quality improvement must be given by the management. Besides this, the quality planning and quality policy, resource management, proper internal communication, and management review should be developed by the management. Each step in the lifecycle of a drug must be carefully handled. The description of each step must be denoted during the process management. The risk management method must be described. For the zero-defect product, the validation program should be introduced, which results in the continual improvement of the whole pharmaceutical system.

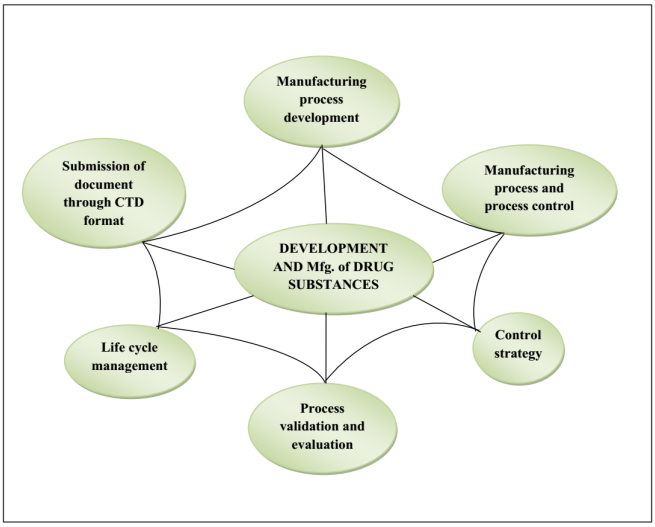

Figure 7: Manufacturing of drug substances model

Regulatory Model for ICH Q11 Guidelines

ICH Q11 states about the development and manufacturing of drug substances (Figure 7). It consists of a total of six parameters. For the ICH Q11 guideline, we proposed a spider modeling system. The parameters which are played a vital role in the development and manufacturing of drug substances are manufacturing process development, manufacturing process and its control, control strategy, process validation and evaluation, life cycle management, submission of document through CTD format.[19]

Evaluation

The manufacturing of drug substances started from the development of the process for the particular drug substances. The development process should be defined, justified, minimum risk-oriented, and productive. The developed process must be efficient to produce the quality product at the end. The control of the process in every step must be clearly described and justified and the variables along with their reduction process should be notified in the change control. The strategies which are implemented to control of the process must be useful and justified. Continuous evaluation and process validation must be done for continual improvement and to avoid hazards. During lifecycle management, all probable necessary steps should be taken. Avoid the risk, healthy management procedure, overall communication in the industry, flexibility in regulation leads to the timely submission of the documents. The simple format of the common technical document also provides flexibility in submission. Nowadays, it changes to electronic common technical documents, leading to more security and safety of the whole procedure's data management system.

Development of Regulatory Models according to the Indian Guidelines

The Indian guidelines i.e., Drugs and Cosmetics Acts and Rules 1945, are thoroughly studied and found that there are some probable elements in Schedule M, Schedule M-III, Schedule L-I, and Schedule Y. From these Indian guidelines, two models are prepared (Figure 8).

Schedule M

Schedule M of "Drugs and Cosmetics Rules 1945" describes Good manufacturing practices.[20] After going through Schedule

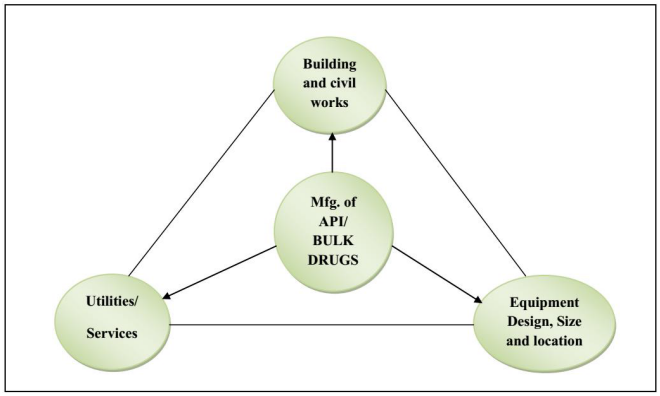

Figure 8: Regulatory models for manufacturing of API/bulk drugs

M we found the elements in PART 1-F of Schedule M under Drugs and Cosmetics Rules 1945, which may produce the guidelines for QbD. Schedule M of Drugs and Cosmetics Rules 1945 describes the Specific Requirements of Premises, Plant and Materials for the manufacture of Active Pharmaceutical Ingredients (Bulk Drugs)." The elements mentioned in the PART-1F of Schedule M are building and civil works, utilities/ services, equipment design, size, and location.[21] By taking the consideration of the elements of PART -1F a probable triangular model is developed for the above guideline.

Evaluation

The production of bulk drugs generally depends on three elements as per Indian guidelines that directly relate to the main elements as per the proposed model. For the production of the active pharmaceutical ingredients, there should be the proper building facilities where the whole process can be easily performed. The manufacturing area's space must be wide and along with the proper exhaust system and recirculation system to control the contamination during manufacturing. For the final stage preparation, pre-filtration systems are included with a 5-micron filter. The atmosphere i.e. temperature, humidity should be under control based upon the specification of drugs. Besides this, there should be sufficient equipment facilities for production. The utilities and services are also describing about equipment facilities. The equipment and other utilities that are used must be cleaned, validated, and maintained to prevent contamination from eliminating the interference in the safety, identity, strength, quality, and purity of the drug products. According to the size of the batch, equipment must be selected. The appropriate design for equipment must be selected and it should be located in a suitable position where there is a smooth facility in operation and easily maintained by the personnel. The justification behind the cleaning procedure must be described. There should not be any kind of hazardous substances where the equipment was installed.

Schedule M-III

Under the "Drugs and Cosmetics Rules 1945" Schedule M-III describes the Quality management system for medical devices and in vitro diagnosis.[22] In point number 4 of Schedule M-III there is the regulation for a quality management system that may have the capability to produce the healthy guidelines for the QbD through its basic elements. The four main efficient elements that generally can develop the guidelines are quality planning, quality policy, management responsibility, and customer satisfaction.

Evaluation

For the quality management system, a circular model is proposed where the quality management system is directly connected to its four elements. For a healthy quality management system at first, planning is required. To achieve the required quality, the management should have proper planning of work. Communication from the upper managerial level to the lower managerial level must be healthy. There should be a top-down and bottom-up approach in the employee relation system. The descriptions of the whole process, the strategy of achieving the goals, the steps which will be taken to achieve the quality are generally discussed in the quality planning. The quality policy generally describes the proper manufacturing facility, commitment towards the effective quality management system, making the framework for establishing and reviewing the quality objectives along with reviewed for continuing suitability. For the fulfilment of these two parameters management plays an important role. To implement these two objectives, management should build up a healthy network among all the departments of the company. By fulfilling these quality parameters, the whole quality management system can be improved through continuous reviewing, proper documentation, and several auditing types, which makes maintaining the TQM. Comprehensive quality management is responsible for continual improvement, which finally helps achieve the zero-defect product and ultimately justify the fourth element, customer satisfaction.

Schedule L-I

Schedule L-I of Drugs and Cosmetics Rules 1945 describes the GLP i.e. Good laboratory practices which may be included for producing the guidelines for the QbD. It complies with rule number 74, 78, and 150 E. There are 16 parameters for the GLP including a huge number of sub-points. The parameters are the following 1. General requirements, 2. Premises, 3. Personnel, 4. Equipments, 5. Chemicals and reagents, 6. Good housekeeping and safety, 7. Maintenance, calibration and validation of equipment's, 8. Reference materials, 9. Quality system, 10. Internal quality system audits, 12. Management review, 13. Standard operating procedures, 14. Protocols and specifications archive, 15. Raw data, 16. Storage and archival.[23]

Schedule Y

Schedule Y of Drugs and Cosmetics Rules 1945 stated about the requirements and guidelines for permission to import and/or manufacture of new drugs for sale or to undertake clinical trials under the rules number 122A, 122B, 122D,

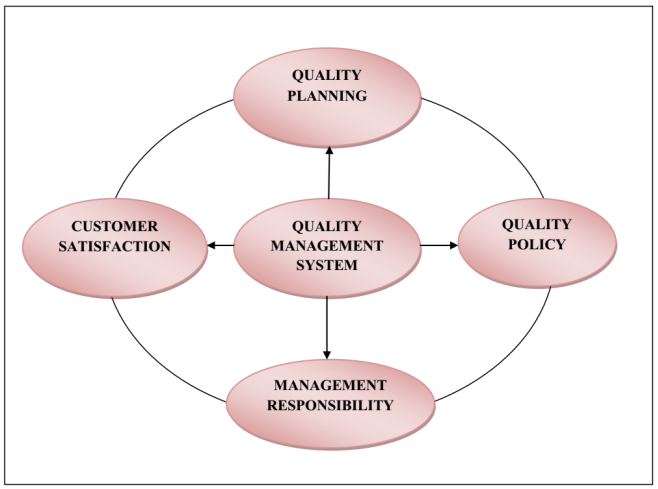

Figure 9: Regulatory models for quality management system

122DA, 122DAA, 122E. The appendix-I of schedule Y clearly stated the "data to be submitted along with the application to conduct clinical trials/import/manufacture of new drugs for marketing in the country".[24] It may be beneficial to produce the guidelines for the QbD. as the product information and understanding is one of the vital parameters for QbD (QbD), the data regarding the drug products available in these guidelines can play a significant role in QbD. This appendix-I has a total of 12 points; among these 12 points, point number 2 describes the "chemical and pharmaceutical information."[25] The description of the whole drug product is a vital aspect of QbD as it helps to measure the critical aspects of the product.[26] The biopharmaceutical aspects also depend upon the drug description and both critical measures and biopharmaceutical aspects included in QTPP.[27] It describes the several data which give sufficient information about the QTPP. Here we proposed a tabular model for the parameters of the drug products.

Comparison Study

After studying both of the guidelines and developing the possible regulatory models for both of the guidelines, the overall comparison study is done to check out the difference between the developed models, guidelines, parameters/ elements of QbD.

DISCUSSION

After a study of two guidelines total of nine probable models were proposed, seven models from ICH guidelines, and two

SL NO.	SUBJECTS	INFORMATION
2.1.	Information on active ingredients	Drug information (Generic Name, Chemical Name)
2.2.	Physicochemical Data	(a) Chemical name and Structure Empirical formula Molecular weight (b) Physical properties Description Solubility Rotation Partition coefficient Dissociation constant
2.3.	Analytical Data	Elemental analysis Mass spectrum NMR spectra IR spectra UV spectra Polymorphic identification
2.4.	Complete monograph specification including	Identification Identity/quantification of impurities Enantiomeric purity Assay
2.5.	Validations	Assay method Impurity estimation method Residual solvent/other volatile impurities (OVI) estimation method
2.6.	Stability Studies	Final release specification Reference standard characterization Material safety data sheet
2.7.	Data on Formulation	Dosage form Composition Master manufacturing formula Details of the formulation (including inactive ingredients) In process quality control check Finished product specification Excipient compatibility study Validation of the analytical method Pack presentation Dissolution Assay Impurities Content uniformity pH Force degradation study Stability evaluation in market intended pack at proposed storage conditions Packing specifications Process validation

Figure 10: Tabular model for chemical and pharmaceutical information

Table 1: Comparison between the developed models

ICH Guidelines	*Indian Guidelines*
Four regulatory models have successfully developed four guidelines.	Only two regulatory models are developed from the selected guidelines.
For the Pharmaceutical development, three sub-models are developed	Based on selected guidelines no sub-models can't be developed.
Flexible regulatory models can be developed as guidelines are flexible.	Due to rigidity in guidelines, the flexible regulatory models cannot be prepared.
The six vital elements regarding design space are mentioned that helps to develop the hexagonal model for design space.	No elements for design space are proposed that's why any model cannot be prepared for design space
The research elements are mentioned that's why the sub-model for research elements is possible to develop.	No research element parameters are mentioned. Due to this reason, the sub-model for research development is not possible
The quality risk management model is developed from quality risk management guidelines for the estimation and ranking of the risk.	The guidelines or elements for the risk management system are not described from the aspects of Indian guidelines, so model development is not possible.
Pharmaceutical quality system model is developed.	Only the QMS model can be developed.
Variables and their relation with control strategy can be described clearly through a modeling system.	A huge long list of controls in GLP is proposed. So, model development is not possible.
As all clear steps are mentioned for mfg. of drug substances, so the spider model can be prepared.	Only three elements are proposed so the triangular model is prepared.

Table 2: Model comparison Comparison between the parameters/ elements of QbD

ICH guidelines	*Indian guidelines*
Sufficient information provided for performing a QbD.	Less information given and not particularly mentioned the parameters.
Approaches are very simple and easy to understand.	Complicated approaches.
Parameters for pharmaceutical development like CMA, CQA, QTPP, CPP are mentioned clearly.	These parameters are missing in the Indian guidelines.
Guidelines for risk assessment are mentioned which is a key parameter of QbD.	No such kind of things are included
Descriptions of QTPP parameters are very simplified.	More characteristics and information regarding drugs are given, which may help to develop the QTPP for QbD as per the Indian concept.
All steps of the manufacturing of drug substances are mentioned	Only the requirement of production of API/drug substances are mentioned

Table 3: Element comparison Comparison between the guidelines

ICH guidelines	*Indian guidelines*
ICH is a harmonized guideline that describes all aspects of the pharmaceutical sectors.	Indian guidelines are stating regarding the finished pharmaceutical products and their processing.
It is accepted all over the world.	It is only accepted in India.
It is regulated by international bodies.	It is regulated by the CDSCO the regulatory body of India.
There is a wide flexible range of ICH guidelines.	The flexibility range is lesser than the ICH guidelines.
ICH guidelines are the independent guidelines.	All the Indian guidelines are coming under the "Drugs and cosmetics act and rule 1945".
Updated according to the need of present market scenario and as per the demand of pharmaceutical sectors.	Amended according to the time to control and prevent the misuse of pharmaceutical products.

models from Indian guidelines. Two types of guidelines and proposed models are successfully compared, and the deficiency in the Indian guidelines is stated in the comparison study by taking the ICH as standard. There are some deficiencies in elements as well as inflexibility are found in Indian guidelines, which is mentioned in the comparison table. The Indian guidelines have the elements to produce the healthy QbD guidelines but it needs some improvement to increase its efficiency. The following deficits were observed on doing the comparison study, and accordingly, recommendations were made to make it proper for ensuring the quality of the product-

a. There is no description of research elements like QTPP, CQA's, and CQA risk management in Indian guidelines.
   Recommendation: This parameter should be included in the APPENDIX- I and APPENDIX I-A of "Schedule Y" as well as in "Schedule M."
b. As QbD is a flexible approach, there must be the design space is needed to produce healthy QbD guidelines. But there are no such guidelines that can describe the design space.
   Recommendation: These design space parameters should be included under the point 7.3 and 4 of "Schedule-M-III" where "Design and development" and "Quality Management System" is described.
c. The flexible regulatory approaches are not given in any of the chosen guidelines which may have the capability to produce the guidelines for QbD.
   Recommendation: The parameters of a flexible regulatory approach should be included under the PART-I of "Schedule-M" in which "General Requirements" are described.
d. The guidelines are not harmonized with each other. There should be a common aspect & relation between the guidelines besides this; they are too long and critical to understand.
   Recommendation: A common technical information system should be included to summarize the selected guidelines.
e. There are no "Quality Risk Management" guidelines in the Indian regulation.
   Recommendation: Separate Schedule needs to be introduced in the Drugs and Cosmetics Rules, 1945.
f. All parameters regarding the Risk management procedure are missing in the guidelines.
   Recommendation: The all tools of Risk management like assessment, evaluation, analysis, control, the reduction should be included in point 14 of "General requirements" under the PART-I of "Schedule M" and the documentation of Risk Management should be included under the point 12.
g. The procedure of manufacturing of the API/Bulk drugs is not given. Only requirements are mentioned.
   Recommendation: The procedure should be mentioned in PART 1-F of "Schedule M."
h. The information regarding drug in APPENDIX-I of "Schedule Y" are not described in an organized way.
   Recommendation: There should be an organized format for taking as the characteristics of the parameters of the drug.
i. The parameters for new drug substances are given but the documentation procedure during application is not described in "Schedule Y".
   Recommendation: The eCTD or CTD should be including in the APPENDIX-I of Schedule-Y.
j. The overall guidelines are too rigid and complex. The flexibility is not provided to the guidelines. It contains a large number of sections, points, sub-points, appendixes, parts, subparts.
   Recommendation: The guidelines requires a summarized version, and frequently using and, our, / together should be reduced.

CONCLUSION

The models were successfully developed from both of the guidelines. The seven models are developed based on ICH guidelines and only two models are prepared from the Indian guidelines. The comparison studies of both the developed models, elements and guidelines shows that there are elements present in Indian guidelines and the development of guidelines for the QbD are possible. But comparison study also reflects that some major elements of QbD are also missing in the Indian guidelines, which are also essential to develop the guidelines of QbD as per Indian aspects. The probable recommendations are given for the correction of gap in Indian guidelines. We hope our suggestions will be considered to develop healthy guidelines for QbD from Indian aspects.

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