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APPLICATION OF RISK ASSESSMENT IN PRODUCT QUALITY LIFECYCLE MANAGEMENT

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ABSTRACT

Quality risk assessment refers to the process of identification of hazards, analysis and evaluation of risk associated with its exposure. Once a potential risk is identified, then appropriate risk control strategies can be implemented to minimise the potential risks. Traditionally, risk assessment is an integral part of Good Manufacturing Practice guidelines from "The Pharmaceutical Inspection Cooperation Scheme (PIC/s)" and "European Medicines Agency (EMA)". Subsequently, the International Conference on Harmonisation published a series of guidelines to harmonise the requirements which covers Q1 which covers stability to Q11 which talks about development and manufacture of drug substance. This includes (ICH) Q9- Quality Risk Management which explains the systematic ways to perform risk assessments, and Q10-Pharmaceutical quality system which talks about control strategy and continual improvements in the product lifecycle. There are a handful of new guidelines and requirements in pipeline which affects the pharmaceutical industry in near future. ICH Q3D Guideline for Elemental Impurities will be implemented globally with in next few years and for this, a systematic risk assessment for risk due to elemental impurities is required to be conducted. Similarly, a new guideline by ICH for Pharmaceutical Product Lifecycle Management (Q12) will also ride on similar risk assessment principles. Therefore, there is a need to develop a holistic approach for product quality risk management which can be applied from development of control strategy to its maintenance as a part of life-cycle management of the medicinal product.During development, the risks from the materials, equipment and process development studies is considered for the development of a control strategy whereas in post approval, changes such as suppliers, equipment, process etc. can influence the product performance and risk profiles. There should be an adaptive risk assessment model which helps in continuous updating of the control strategy. This article is to provide an overview of changes happened in thequality risk assessment approach and its current applications during the development and lifecycle management of pharmaceutical products and continuously updating control strategy.

Keywords: Quality risk assessment, Product quality lifecycle, Quality risk management

INTRODUCTION

The concept of product lifecycle management originates from automobile, defence and aerospace industries to automate their processes and data management. In a pharmaceutical quality system and in its implementation thorough out the different stages of lifecycle, quality risk management is a fundamental part. Risk assessment is the key component of International Standards Organisation (ISO) quality concepts, Good Manufacturing Practice guidelines from "The Pharmaceutical Inspection Cooperation Scheme (PIC/s)" and "European Medicines Agency (EMA)".

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Subsequently, the International Conference on Harmonisation published a series of guidelines to harmonise the requirements which covers Q1 which covers stability to Q11 which talks about development and manufacture of drug substance. This includes (ICH) Q9- Quality Risk Management which explains the systematic ways to perform risk assessments, and Q10-Pharmaceutical quality system which talks about control strategy and continual improvements in the product lifecycle.

Principles of risk management are applied in almost every segment like insurance, finance, public health and pharmacovigilance for the lifecycle management of products [1]. In pharmaceutical sector, every new drug applications are thoroughly assessed for balancing the desirable clinical effects (benefits) and undesirable clinical effects (risks) of drugs is the core task of drug regulatory agencies (benefit-risk assessment)[2]. The risk management principles are also being widely implemented in the pharmaceutical manufacturing industry to improve quality of the products with the introduction of

guidance by ICH Q9-Quality Risk Management [1] and introduction of 'quality risk management" under chapter 1 of PIC/s GMP guide [3]. There are many new guidelines and requirements introduced since then, riding on the same risk management principles.

Quality risk management isa systematic process for the assessment, control, communication and review of risks to the quality of the medicinal products across the product lifecycle [1-3]. Although many models can be used for quality risk management, the model outlined in ICH Q9 guidance received wide acceptability. This model consists of risk assessment, risk control, and risk review as the key steps of the risk management process.

As per Annex-II of ICH Q9, there are several potential areas listed where the principles of quality risk management are required to be applied to the pharmaceutical manufacturing. Another ICH guideline "Q3D Guideline on Elemental Impurities" will be implemented for new applications soon and for existing products in near future. ICH Q3D mandates all manufacturers to perform risk assessment for the elemental impurities that may carry over to the final product from materials and equipment. Similar risk assessment principles were applied also for the microbial quality testing to decide omission or skip-lot testing in the control strategy [6]. A new guideline for lifecycle management – "ICH Q12 lifecycle management" [5] is being drafted which is also based on the same risk management principles.Therefore, there is a need relook into the application of quality risk management in product development to make a control strategy and its maintenance throughout product lifecycleusing the same risk management principles.

AN OVERVIEW OF PRODUCT QUALITY LIFECYCLE:

The concept of quality risk management is increasingly being applied in the product quality lifecycle to achieve the objectives such as process understanding, maintain a steady state of control and to facilitate continuous improvement [5-7]. A typical product quality lifecycle have three phases- namely, process development, development of control strategy, and continual improvement of the product.

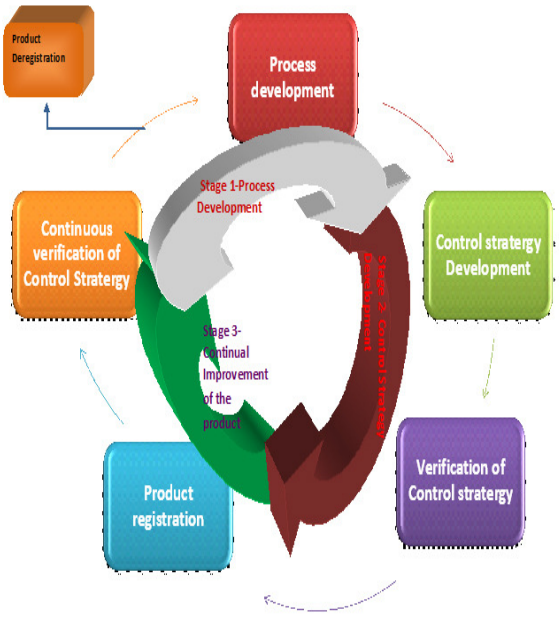


Figure- 1: Overview of Product quality Lifecycle

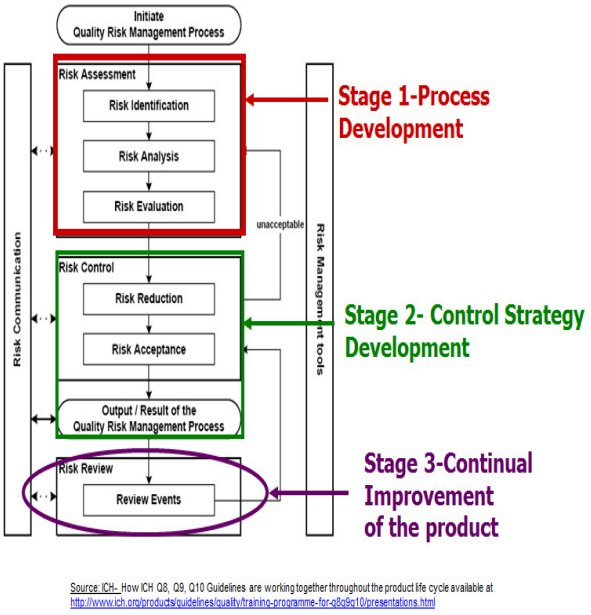
Process understanding is achieved in the pharmaceutical development by conducting a series of studies and by applying the ICH Q9 risk management principles to assess the resultant data. All potential risk factors are identified, analysed and the results were evaluated to achieve Quality Target Product Profile (QTPP). Relevant Critical Quality Attributes (CQAs) can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product [8]. These were translated into control strategy in-order to control the risk at an acceptable level.

A control strategy is designed to ensure that a product of required quality will be produced consistently [8]. The potential sources of variability which have an influence on the product quality is identified, have a process understanding, and finally controlled in control strategy. Additionally, the manufacturers prior experience in the manufacturing of similar products also will add value to this assessment.

For a normal drug product where complex real time testing or multivariate prediction models were not applied, a control strategy generally includes, but is not limited to, the following:

- Control of material attributes- API and excipients;
- Drug product specification;
- Critical Process Parameters;
- GMP controls

It is also necessary to consider several available guidelines in deciding the risk acceptance. This proposed risk controls need to verify as well. The outcome of this quality risk management process will be an effective control strategy and successful product registration. This facilitate in the maintenance of state of control. Post marketing of the product, an effective risk management plan will be there to review the risk that rose due to changes in quality of input materials, process or equipment changes and/or changes to good manufacturing practices. The data from the periodic review programs used to detect any unintentional variations and find out continual improvement opportunities.



Source: ICH- How ICH Q8, Q9, Q10 Guidelines are working together throughout the product life cycle available at http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html

Figure-2: Quality risk management process-ICH Q9

STAGE 1: PHARMACEUTICAL DEVELOPMENT

A systematic risk assessment is performed during the product development to develop a robust control strategy. The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and healthcare professionals, and regulatory authorities [7]. Generally, for a formulation, active pharmaceutical ingredients, excipients, and manufacturing process can influence the final product quality. Therefore a careful identification of the risk factors contributing to the final control strategy and studies to determine the impact is needed to be studied in the product development.

Figure-3: Factors affecting pharmaceutical development

RISK IDENTIFICATION

Risk identification refers to the systematic process of using the information to identify potential hazards. Information used for this purpose can include manufacturers' historical data, theoretical analysis, stakeholders' feedback, informed opinions and general regulatory requirements for the dosage form set in various guidelines such as ICH and pharmacopoeias.

The factors affecting the product quality is depending upon the dosage form. In general, the factors that have potential impact on the product quality are a) impurities, b) manufacturing process, c) microbial quality, and d) environment and GMP (Good Manufacturing Practices). There are lot of guidelines available which helps in the risk identification and risk control.

The risk due to impurities arises from the materials used in the formulation and those arise during manufacturing process. Generally the risk factors that need to be considered for the development of control strategy include a) elemental impurities, b) impurities due to compatibility of ingredients and d) degradation products.The formulation gets elemental impurities from the ingredients used as well as from

the equipment which comes in contact with the product. The new guideline ICH Q3D [4] provides a list of elemental impurities which need to be considered during the product development.

The target of pharmaceutical development is to make a product meeting the intended Quality Target Product Profile with satisfactory stability. During this process, critical quality attributes and critical process parameters that are essential for the product performance need to be identified. Unless the proposed product is a specialised dosage form, the universal tests and acceptance criteria stated in ICH Q6A[9] can be considered based on the dosage form. In addition, the input material quality is also need to be selected for the development studies. For example, the study of particle size and its impact on the product performance.

Microbial quality should also be monitored in all pharmaceutical preparations. All sterile preparations should meet the sterility and endotoxin requirement required based on the daily dose. To achieve this, assessment of input material quality and risks from the process and environment is necessary. This is also required for non-sterile pharmaceutical preparations and for the raw materials used for pharmaceutical preparations [10].

The environment and good manufacturing practices also contribute to the overall product quality of pharmaceutical preparations. The risk factors from these aspects should be identified using the techniques depicted in ICH Q9 guidance. Drug substance GMP practices as described under ICH Q7 guidance is also important and must adhere to and need to be reviewed as a part of supplier qualification. Last but not the least is the manufacturers' prior experience in similar dosage form and similar products. This helps the manufacturer to pre-set lot of factors and conduct development studies more appropriately.

RISK ANALYSIS

Risk analysis is the next stage which is a systematic process of quantification of risks with association to the product quality. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In ICH Q9 guidance, lot of risk estimation tools are provided which can be effectively used to identify the risk related to environment and GMP practices. However, these tools are not adequate for the quantification of other risks. These risks are generally measured using a validated analytical procedure and maximum tolerances are either available in international guidelines or determined based on pharmaceutical development and manufacturers' experience with the dosage form. These risks include a) contaminants which include elemental impurities, microbial quality and degradation products and b) factors that affect product performance.

Contaminants such as elemental impurities, microbial quality and degradation products can originates from the raw materials used in the process. In addition to raw materials, other factors such as equipment, compatibility between the ingredients and equipment parts coming in contact with the product also add contaminants. For example, elemental impurity can occur in the raw materials used which include drug substance and excipients. Equipment contact parts are also contributing the elemental impurities. Therefore, the risk analysis should cover the risk from all these sources. Microbial contamination also happens in the same way but additional factors from environment and GMP can contribute to it. However, these factors are regularly inspected and controlled, a separate assessment for the microbial contamination from the environment and GMP generally not required. Degradation products can present in the drug substance used and the manufacturing process and/or compatibility issues can accelerate this.

Two approaches as recommended in ICH Q3D guidance can be used to analyse the risk due to contaminants- a) individual component approach or b) final product approach. In the individual component approach, each individual components are tested and cumulative effect of the risk from all components and contribution from equipment parts that are coming into contact with the product are considered for the product risk assessment whereas in the final product approach, the final product is tested for the risk factors and used for the risk assessment. In addition to the testing for individual elemental impurities, degradation products and microbial quality using validated testing procedures, additional testing of water activity to understand the microbial susceptibility and testing for compatibility of drug substance with excipients and container closure system is important.

The risk factors affecting product performance is differs based on the type of product and its dosage form. Assay, related substances, uniformity of dosage units and microbial quality forms the basic factors to be included in the control strategy in addition to in-process controls whereas the dosage form specificperformance factors include dissolution testing for oral solid dosage forms, droplet size

estimation/comparison for aerosols, dissolution testing for topical preparations etc. For a generic product, characteristics of the innovator product is studied to determine the quality target product profile. Once a product is developed with comparable QTPP, it is further tested for bioequivalence. The formulation and CPPs of the bioequivalent product is used for commercial production using the thus developed control strategy. For an innovator product, design of experiments (DOE) were conducted to understand the process and multivariate data analysis will be conducted to see the interaction of various factors. Based on these studies design space and control strategy is developed.

RISK EVALUATION

The data collected from the above risk analysis need careful evaluation to develop control strategy. Irrespective of the approach taken for risk assessment, cumulative product level of each risk factors need to be considered for risk evaluation. There are lot of guidelines available for determining the acceptability of the levels and deciding the proper control strategy for each of the factors.

Impurity levels including elemental impurities, degradation products, residual solvents and any new impurities that are either leaching due to equipment/container closure system contact or appears due to incompatibility of the ingredients should not exceed the permissible daily exposure (PDE)[17-19]. PDEs are not same as control threshold. Control threshold should be much tighter than PDEs. The PDEs for elemental impurities are listed in ICH Q3D guidelines whereas the PDEs for other impurities and residual solvents should follow the instructions stated in ICH Q3B and Q3C guidelines respectively.

In ICH Q3D guidance, the control threshold is stated as 30% of the PDE. Although this is stated in context of elemental impurities, it is highly recommended as a general rule for all impurities.If the level of impurity in the product based on analysis is less than control threshold or 30% of the PDE or maximum limit allowed in guideline, no additional controls generally necessary. If the current level is more than the control threshold but less than PDE, the control strategy should include a routine or skip lot testing to ensure continuous compliance of the impurity levels. If the level in the product exceeds the acceptable PDE, the process or material quality should be improvised to bring the level below the acceptable PDE. In case where thisis not possible, new toxicological studies should be conducted to understand the impact of this high level of impurity based on the dose. In this situation, national regulatory agencies decide the acceptability of the proposed control threshold.

The data collected from the development studies conducted for process understanding such as design of experiments (DOE) for a new moiety as well as the development study outcome from a pilot batch based on innovator formula and results from pilot BE and commercial upscale data which is generally the case for a generic will also be evaluated in this stage. If a DOE studies were conducted, such data form the basis of control strategy to decide the critical process parameters for control strategy. A design space if developed based on such studies as well as other CPPs forms the part of control strategy.

STAGE 2: CONTROL STRATEGY DEVELOPMENT

Any risk factors, if found above the acceptable limits, the next step is to explore the possibility of risk reduction or risk control. The impurities can be minimised by selecting an alternate source or process improvements for the starting materials by implementing a tighter starting material specification limit for the source of impurity. If the process parameters not meeting the expectations set in pharmacopoeia or QTPP, the process needs to improve to meet the expectations. If the risks cannot be controlled below the maximum acceptable limits, a set of studies such as toxicological studies for impurities should be conducted to evaluate the impact of such risk on the target patient population for that particular dosage.

This final control strategy is verified during process validation and submitted to international regulatory agencies for registration. The guidelines from USFDA, EMA and ASEAN can be referred in the development of a validation protocol and its execution. In addition to general validation guidance available in the above mentioned sources, dosage form specific validation requirements such as for products sterilised by terminal sterilization or aseptic sterilization methods are also available in the same sources.

STAGE 3: CONTINUAL IMPROVEMENT OF THE PRODUCT- APPLICATION OF RISK ASSESSMENT TO THE LIFECYCLE MANAGEMENT

The main emphasis of the ICH guidelines so far was on early stages of product lifecycle i.e. before registration. Although there was lot of ICH guidelines such as Q8 to Q11 being applied to post

launch quality management, there was no harmonised approach and new ICH guideline Q12 is coming to fill this gap [5]. Although the complete picture is only available after publication of this guideline, the concept is already available in ICH Q3D about application of risk assessment principles in life cycle management. Therefore the new ICH Q12 is expected to provide greater clarity in the requirements and no major changes are expected.

After the product launch, the product will be affected by the risks from suppliers, process and good manufacturing practice related issues such as personal, environment, quality system etc. A proper risk management is required for periodic review of these risk factors and perform necessary changes to the control strategy and/or possibility of risk control measures. In an ideal scenario, possibility of additional risk control measures need to be explored before making changes to the control strategy.

Figure-3: Factors affecting control strategy

CHANGES AND VARIABILITY

After the product launch, the product will be subjected to changes and variability. For a known change, a well prepared documentation covering the description, justification for the change, its implementation plan and finally its impact on the product performance and patient safety need to be prepared. A clearer procedure required when this mandate a new development studies including the process development, validation and stability as well as the risk assessment for the impurities and contaminants.

Post commercialization, the process is also likely to encounter new sources or variation which is not anticipated before or to which the process is not previously exposed [11].

A continued process verification program (CPV) [12] is a requirement as a part of the new process validation concept. This means that all processes remain in the same state of control as in the development stage. All sources of process variables cannot be anticipated and such unanticipated trends which can only be identified using an effective CPV program which can highlight the process improvement opportunities. Continuous adjustments to the process compensate for process variability ensuring that the final product remains in the state of constant quality.

Management of such variability can only be performed using the risk management principles. For applying the risk management for addressing the variability need a better understanding of the origin of such variability, the range and its impact on the intended process, final drug product and most important , on the end user- the patient. A product specific CPV plan also need following elements [12]:

a) Clearer role and responsibilities for the organisation.

b) A scientifically sound sampling/testing plan.

c) Statistical data analysis methods.

d) Defined acceptance criteria

e) Clear procedures for managing OOT and OOS.

f) Clearer understanding on the process changes/trends that need going back to development stage.

g) Periodic re-evaluation of CPV.

Timely risk identification and risk control post marketing is a challenge to many multinational pharmaceutical companies. Periodic requalification of suppliers is essential for timely detection of changes in material quality. Nowadays, there is an increasing focus on the GMP for active substances and many API manufactures received noncompliance status as a result of GMP inspection from authorities such as USFDA and EU member states. Since these are publically accessible information, these can become the pool of information for risk assessment. If any of such issues are noticed, the drug product manufacturer's risk assessment should cover the issues identified by the

regulatory authority, any risk mitigation such as complete testing at retesting implemented at drug product manufacturing site and finally, the impact of these on the final product. Tough decisions such as product recalls is common nowadays due to such issues [14, 15]. Uninformed changes to the material quality is another risk to the final product. With changes to the material quality, there will be changes in the product performance or increase in the impurity levels such as elemental impurities. A proper supplier qualification based on site inspection and periodic full testing will minimise such risks.

The manufacturing process also will be subjected to periodic unintentional changes due to changes in personals, equipment and input materials quality. A proper statistical annual product review will be an immense pool of knowledge which can highlight sudden or gradual changes in the product performance. A timely investigation into such events can lead to the actual root causes and a readjustment to the control strategy to mitigate the risk.

An another area where many manufacturers fail is in maintenance of quality system which lead to the total failure of GMPs. Timely failure investigation and corrective measures need to maintain the product performance.

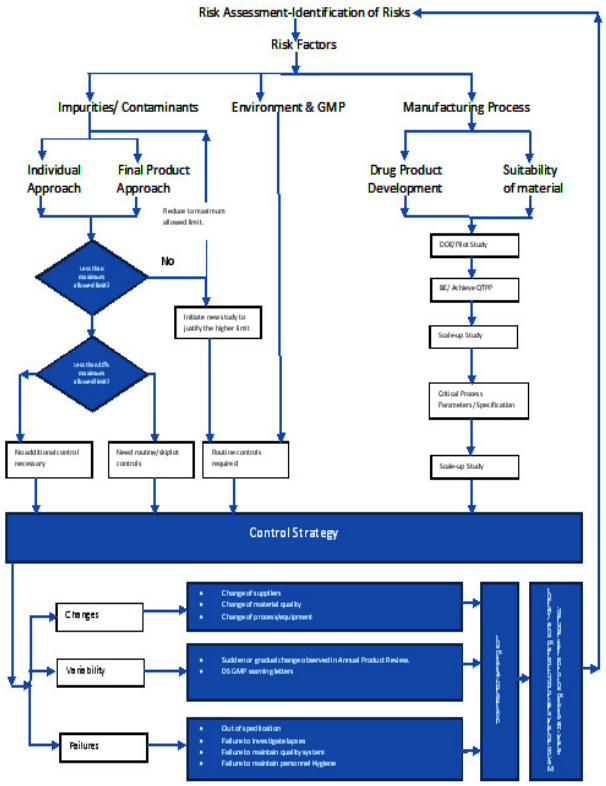


Figure-5: Risk management in product lifecycle

In general, any changes in the manufacturing process that may potentially affect the product performance, and any changes in the equipment or input materials that may elevate the impurities or contaminants mandates the need to redo the risk assessment and risk reduction/measures, if deemed necessary.In all such investigations, opportunities for further improvements and well as possibility of tightening based on the new process understanding gained should also be explored. The risk assessment is a continuous process which starts in the development of a product and continues throughout the product lifecycle for continual improvements for the product. Thus, the flowchart proposed in Fig 5 represents the application of risk assessments at various stages of lifecycle.

CONCLUSION

Risk assessment is now a part of product lifecycle from product development to its end. A systematic risk identification and its evaluation in the pharmaceutical development leading to the development of control strategy and its subsequent verification. After the product launch, a systematic risk identification to detect all changes and variances and should re-evaluate the acceptability of the changes in risk levels and at the same time explore the possibility of tightening and process improvements.These risk management principles forms the core of all new guidelines and its proper understanding and application can minimise the post marketing issues such as product recalls or import ban that many manufacturers face. With the adaptation of ICH Q12, let us hope that there will be clearer methods for the implementation of risk management during the product lifecycle even after its marketing.

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