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Critical parameters in manufacturing process validation of different forms of pharmaceutical injectable products – to assess products' risk framework

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Dissertação

Mestrado em Engenharia Farmacêutica

Master degree in Pharmaceutical Engineering

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“If we do not take change by the hand it will surely take us by the throat.”

Winston Churchill

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Mais uma vez, Obrigada Mãe, Pai e manos.

ABSTRACT

The main goal of this work was to create a valuable Risk Management Approach that enables a Process Validation over products lifecycle. Quality risk management (QRM) has been described in regulatory guidance for several aspects of process validation, such as product lifecycle, extent of validation, determination of critical quality attributes (CQAs) and critical process parameters (CPPs), process design space (DS), and sampling plans and statistical confidence levels. Verification of the process in every single produced batch, over the product life time is now an expectation from regulatory authorities.

Based on this Hikma is required to implement a Process Validation as collection and evaluation of data, from the process design phase and continuing through commercial production phase, establishing scientific evidence that a process is in state of control and therefore capable of consistently and effectively assure product quality. Since pharmaceutical products and processes are complex and multivariate by nature, a scientific understanding of relevant multi-factorial relationships requires risk-based approach. In this context, a risk management approach to assess risk of injectable products manufacturing was created. The aim is to reduce or even eliminate potential failures and make more resourceful and efficient, qualitatively and quantitatively, processes over lifecycle.

The goal was successfully achieved, and a systematic process for the assessment, control, communication and review of risks, targeting the highest quality of an injectable product is now available to be applied - Hikma Process Validation Program of Injectable Products Lifecycle.

Keywords: Quality, Validation, Lifecycle, Risk, Process, Tools

RESUMO

O principal objetivo deste trabalho foi criar uma ferramenta valiosa para uma abordagem de Gestão de Risco que permita Validação de Processos em todo o ciclo de vida do produto. A Gestão da qualidade e do Risco tem sido descrita nos guias regulatórios por diversos aspetos da validação de processo, como o ciclo de vida do produto, a extensão da validação, a determinação dos atributos críticos de qualidade (CQAs) e dos parâmetros críticos do processo (CPPs), espaço de desenho do processo (DS), planos de amostragem e intervalos estatíscos de confiança. A verificação do processo em cada lote produzido ao longo do tempo de vida do produto é agora uma expectativa das autoridades reguladoras.

Com base nisto é necessário que a Hikma implemente a Validação de Processo como uma coleção e avaliação de dados, desde a fase de desenho do processo e continuamente durante a fase de produção comercial, estabelecendo evidências científicas que o processo está em estado controlado e que por isso é capaz de consistentemente e eficientemente assegurar um produto de qualidade. Sendo que os produtos e processos farmacêuticos são complexos e multivariados por natureza, um entendimento científico das relações multi-factoriais relevantes pede uma abordagem baseada no risco. Neste contexto, foi criada uma abordagem de gestão de risco para avaliar o risco da produção de produtos injetáveis. A finalidade é reduzir ou até mesmo eliminar potenciais falhas e facultar ao processo mais recursos e tona-lo mais eficiente, qualitativamente e quantitativamente, durante o seu ciclo de vida.

O objetivo foi alcançado com sucesso, e um processo sistemático de avaliação, controlo, comunicação e revisão dos riscos com o alvo da máxima qualidade do produto injetável está agora disponível para ser aplicado – Programa de Validação de Processo Hikma do Ciclo de Vida dos Produtos Injetáveis.

Palavras-chave: Qualidade, Validação, Ciclo-de-vida, Risco, Processo, Ferramentas

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LIST OF ABBREVIATIONS

AHP	*Analytical Hierarchy Process*
CAPA	*Corrective Action Preventive Action*
CCP	*Critical Control Parameters*
cGMP	*Current Good Manufacturing Practices*
CMAs	*Critical Material Attributes*
CPP	*Critical Process Parameter*
CPV	*Continued Process Verification*
CQA	*Critical Quality Attribute*
DS	*Design Space*
EMA	*European Medicines Agency*
FDA	*U. S. Food and Drug Administration*
FMEA	*Failure Modes and Effects Analysis*
FMECA	*Failure Modes, Effects and Criticality Analysis*
HACCP	*Hazard Analysis and Critical Control Points*
IPC	*In Process Control*
IQ	*Installation qualification*
NOR	*Normal Operating Range*
OOC	*Out-of-control*
OQ	*Operational performance qualification*
PAR	*Proven Acceptable Range*
PAT	*Process Analytical Technology*
PDA	*Parenteral Drug Association*
PQ	*Product performance qualification*
PQS	*Pharmaceutical Quality System*
PV	*Process Validation*
PVP	*Process Validation Protocol*

PVR	*Process Validation Report*
QbD	*Quality by Design*
QRM	*Quality Risk Management*
QRM	*Quality Risk Management*
QS	*Quality System*
QS	*Quality System*
QTPP	*Quality Target Product Profile*
RAMM	*Risk Analysis and Mitigation Matrix*
RTRT	*Real-Time Release Testing*
SAB	*Scientific Advisory Board*
SOPs	*standard operating procedures*

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Chapter 1 INTRODUCTION

Process validation is used to confirm that the resulting product from a specified process consistently conforms to product requirements. A risk-based approach helps to identify crucial parameters as sources of process variation that affect product quality. Controlling the sources of variation commensurate with the risk they represent to the process and final product attributes are the key concepts of assessing products` quality framework.

The next chapter – LITERATURE OVERVIEW – has the purpose of giving the background required to understand the issues addressed in the later chapters, therefore the focus is mainly on process validation, risk management and critical process parameters impact on injectables products quality. Following this, the chapter – PARAMETERS AND METHODS – Quality Risk Management Tools presents general statistical methods and tools for risk analysis and process variability.

Afterwards, in the subsequent chapter – RESULTS – Assess Products` Risk Framework is presented, followed by one section containing the tool application to Hikma products and the discussion of the data, respectively. This work focuses on how a science- and risk-based approach toward process validation can be created and how such an approach can alleviate potential sources of failures. As final chapters, conclusions and future perspective are presented.

The work behind this thesis was performed in Hikma Farmacêutica S.A., Portugal and Thymoorgan Pharmazie GmbH, Germany.

Chapter 2 LITERATURE OVERVIEW

When a new process and product are developed or there is an attempt to understand an existing process, knowing how materials, processes and controls affect the final product is essential (Brindle, et al., 2012).

2.1. Process Validation and Guidelines Chronology

The concept of Process Validation has been changing over the last decades. In 1987 FDA (*U. S. Food and Drug Administration*) issued *Guidance for Process Validation* (Guideline on General Principles of Process Validation, May, 1987) (**Figure 1**) in order to drive industries to reflect on process validation best practices. This Guidance defined the types of validations as Prospective and Retrospective; also defined the IQ (Installation qualification) including subjectively OQ (Operational qualification) and PQ (Process qualification)[1]; and enlightened worst case scenario studies, Process Revalidation and Process Validation as a multiple batch demonstration (FDA, 2009). However, in the latest FDA guidelines this old IQ/OQ/PQ approach doesn`t demonstrate the process itself; equipment function is barely half of the story. There are raw materials and inputs, process controls, and product attributes associated with every unit operation in a manufacturing process.

In the past, the types of process validation were defined in terms of when they occur in relation to product design, transfer to production and release of the product for distribution. *Prospective validation* was defined as the validation carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps: these are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. *Retrospective validation* was a concept that used to involved the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analyzed to determine the limits of process parameters. A trend analysis used to be conducted to determine

1 **Installation qualification (IQ):** establishing documented evidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. **Operational performance qualification (OQ):** establishing documented evidence that the process is effective and reproducible. **Product performance qualification (PQ):** establishing documented evidence through appropriate testing that the finished product produced by a specified process(es) meets all release requirements for functionality and safety (FDA, 2009).

the extent to which the process parameters are within the permissible range. Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products.

Also, 1987 guidance included the concept of revalidation of processes when changes to a process are introduced, or when process variation is detected. *Revalidation* ensured that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality. A Revalidation could be performed after any change having a bearing on product quality or periodically carried out at scheduled intervals.

But the concept of worst-case conditions for Process validation was a key theme of the 1987 guidance – "A set of conditions encompassing upper and lower limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions.

The basic Principles for Process Validation according to 1987 Guidance on General Principles of Process Validation can be stated as follows:

- Establish that the process equipment has the capability of operating within required parameters;
- Demonstrate that controlling, monitoring, and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment;
- Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operated within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and
- Monitor the validated process during routine operation. As needed, re-qualify and recertify the equipment.

The most recent approach (Guidance for Industry - Process Validation: General Principles and Practices, January 2011) describes three stages of process validation during the lifecycle of a drug, which falls into ICH Q8 (Guidance for Industry - Q8 Pharmaceutical Development, May 2006) (**Figure 1**). During early product and processes development, process design builds criteria for testing, qualification, and setting specifications on. Process qualification encompasses many validation concepts familiar to those who have been working with the previous guidance document all along: Manufacturing equipment, tooling, and instrumentation, and utilities must be qualified using standard validation protocols along with an associated validation master plan, risk assessment, and requirements specifications. Continued process verification, the final stage, is the ongoing assurance gained during routine production that the process remains in state of control (*Section 2.4 - Manufacturing Process Validation over Products Lifecycle*).

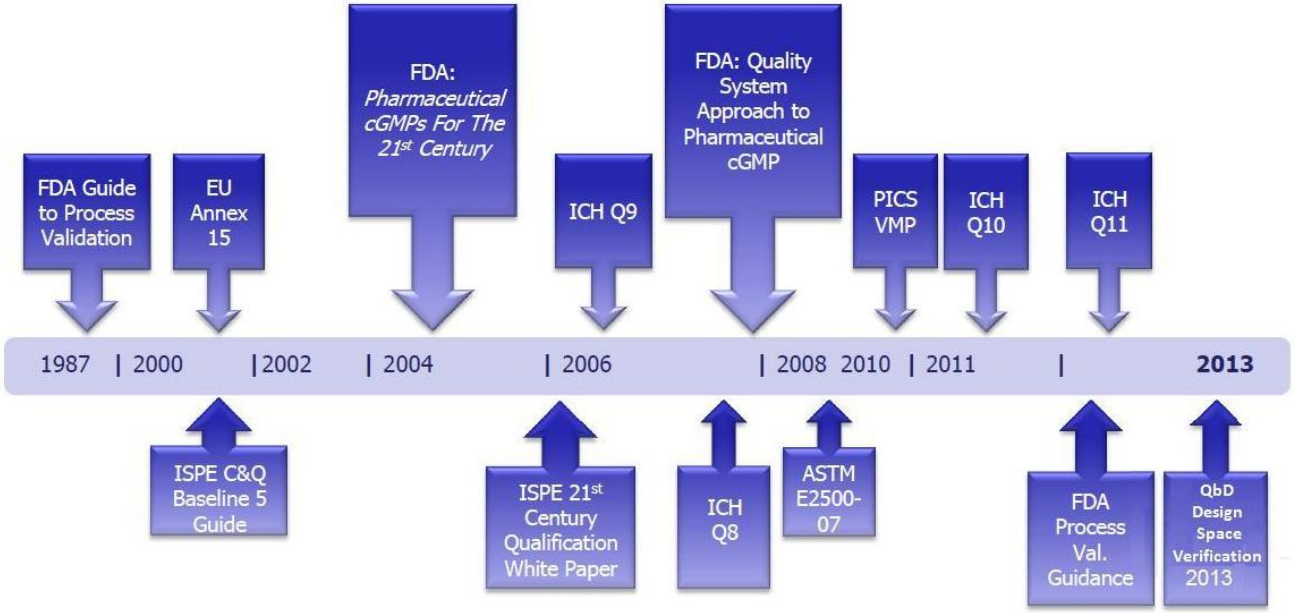


Figure 1: Chronogram of Process Validation and risk concept evolution.

After some years in which companies applied this 1987 guideline, there was one question still to be answered: *If validation provides a high degree of assurance that the process works reliably and predictably, then why do processes fail during commercial manufacture?* And the answer was afterwards clear - *Process Variation.*

In 2006 FDA notified industry, and issued, in draft Nov. 17, 2008 "reflection of industry practice" and PDA (*Parenteral Drug Association*) SAB *(Scientific Advisory Board)* formed a committee to collect and collate member comments. In January, 2011 FDA issued new guidance for industry regarding process validation (Guidance for Industry - Process Validation: General Principles and Practices, January 2011) (**Figure 1**).

In the past, process validation emphasis has been on collecting large quantities of data from process validation batches, leading to a perception of process validation as largely a documentation exercise. The updated approach requires the manufacturer to collect data through the product lifecycle and evaluate it for evidence that it supports a quality and in state of control process.

The 2011 guidance revised the concept of revalidation of processes with the introduction of Continued Process Verification (*Section 2.4.3 - Stage 3: Continued Process Verification (CPV)*). Also Retrospective validation is not mentioned. The worst case concept was removed and the expectations changed, as follows:

The commercial manufacturing process and routine procedures must be followed. The Process Qualification batches (equivalent to their previous name "Process Validation batches") should be manufactured under normal conditions by personal expected to routinely perform each step of each unit operation in the process.

Nowadays, Process Validation is focused on product quality through processes understanding and control: “Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production which establishes scientific evidence that a process is capable of consistently delivering quality product.”(Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

In summary the significant changes from the last approach for process validation are listed below and are also detailed on *Section 2.4 - Manufacturing Process Validation over Products Lifecycle*.

- Add emphasis to process design;
- Include discussion of risk;
- Involve activities over the entire process lifecycle (ongoing program, in three defined stages);
- Emphasizes the role of objective measures and statistical tools;
- Emphasizes the knowledge, detection and control of variability.

EMA (*European Medicines Agency*) published the long-announced revision of its Guideline on Process Validation as draft on March 2012. The final version will replace the current guideline "Note for Guidance on Process Validation (CPMP/QWP/848/96, EMEA/CVMP/598/99). The aim was to include modern aspects of GMP. The concept paper has mentioned **ICH Guidelines Q8** (Guidance for Industry - Q8 Pharmaceutical Development, May 2006), **Q9** (Guidance for Industry - Q9 Quality Risk Management, June 2006) **and Q10** (Pharmaceutical Quality System - ICH Q10, 2011), Process Analytical Technology (**PAT**), Quality by Design (**QbD**), Real-Time Release Testing (**RTRT**). It has already been announced that the revision will add an "enhanced" approach and "continuous process verification" to the current traditional approach as described in ICH Q8 (Guidance for Industry - Q8 Pharmaceutical Development, May 2006). The annexes of the current Note for Guidance will be included in the revised guideline and a harmonisation with the current FDA Guidance on Process Validation is recommended (Pommeranz, 2012). Some differences exist between the issued FDA guidance and the draft of the EMA guideline.

In the last months FDA recommended to the pharmaceutical industries to have Operational Metrics systems under their pharmaceutical quality system. In a different angle but with the same aim (ensure product quality at commercial scale) FDA proposes Design Space Verification.

2.2. Process Validation Key Concepts

Manufacturing Process is "the sequence of activities, people, and systems involved in achieving some desired result".

Operating Parameters are the conditions under which a process is performed. This conditions can be physical or chemical (pH, temperature, pressure, agitator rpm, flow rate, etc.). Process parameters are usually controlled within defined operating ranges to set-point values.

There are some measured product attributes that are deemed critical to ensure the quality requirements of either an intermediate or final product. The identified attributes are termed **Critical Quality Attributes (CQAs)** (Process Robustness - A PQRI White Paper, 2006). CQAs are the physical, chemical, biological, or microbiological property or characteristic that should be within a predetermined range to ensure the desired product quality (Guidance for Industry - Q8 Pharmaceutical Development, May 2006). Not all process outputs (acceptance criteria and specifications) are CQAs.

During development, process characterization studies identify the **Critical (or Key) Process Parameters (CPPs).** Critical Process parameters is a process input that, when varied beyond a limit range has an impact with significant influence on a critical quality attribute (CQA) and therefore should be monitored or controlled to ensure that the process produces the desired quality (**Figure 2**) (Guidance for Industry - Q8 Pharmaceutical Development, May 2006). Failure to stay within the defined range of the CPP leads to a high likelihood of failing to conform to a CQA.

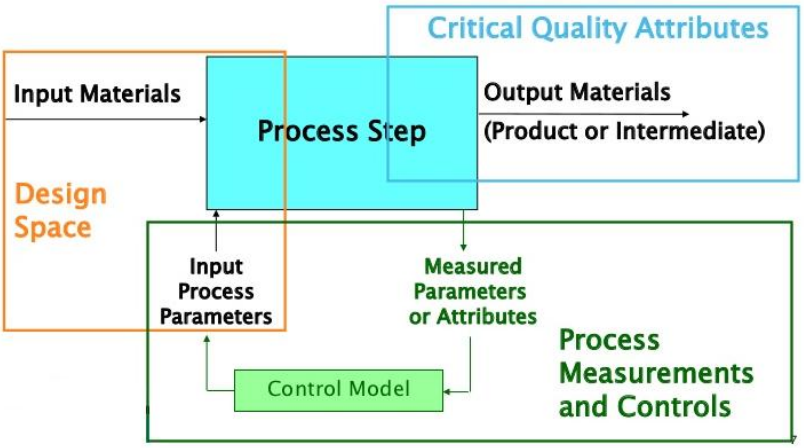


Figure 2: Scheme representing the Process Manufacturing and the relationship between CPPs, Design Space, Controls and CQAs.

It is also important to distinguish between parameters that affect critical quality attributes and parameters that affect the efficiency, yield, or worker safety or other business objectives; those are **Non Critical (non Key) Process Parameters** unless they also impact product quality.

Control procedures shall be established to monitor the output and to validate the performance of those manufacturing parameters that may be responsible for causing variability in the characteristics of in-process material and the drug product (Title 21 - Food and Drugs Chapter I - Food and Drug Administration Department of Health and Human Services subcharpeter C- Drugs - General, April 2013).

Table 1: CPPs and CQAs summing up description

CPPs	CQAs
Typically, set-point with an operating range	Acceptance Criteria / Specifications
Inputs (also raw-materials or components)	*Outputs* (in-process material, intermediates or final product)
Controlled to achieve consistent, repeatable, reliable results	Used to demonstrate process control, repeatability, and reliability

During early stages of a process development, parameter target values and tolerance limits are based on good scientific rationale and experimental knowledge gained from laboratory and pilot scale studies. A parameter that shows a strong relationship to a critical quality attribute becomes a key focal point for further study. In developing the manufacturing science, a body of experimental data is obtained, and the initially selected parameter tolerances are confirmed or adjusted to reflect the data. This becomes the **Proven Acceptable Range (PAR)** for the parameter, and within the PAR an operating range is set based on the typical or **Normal Operating Range (NOR)** for the given parameter (**Figure 3**). PAR becomes the **Design space** if there is a multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide quality assurance (**Figure 5**). Knowledge space is a summary of all process knowledge obtained during product development. Tolerance ranges may be rationalized and adjusted as increased process understanding is gained (Process Robustness - A PQRI White Paper, 2006).

Further study of parameters is a prelude to determining those that are critical process parameters. If varying a parameter beyond a limited range has a detrimental effect o a critical quality attribute, it is defined as a Critical Process Parameter (CPP). A cause-effect relationship may be established for parameters and desired attributes.

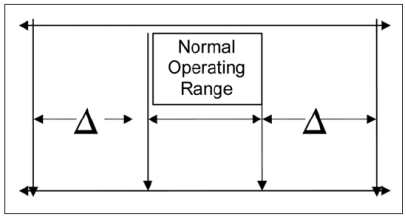


Figure 3: Proven Acceptable Range (PAR).

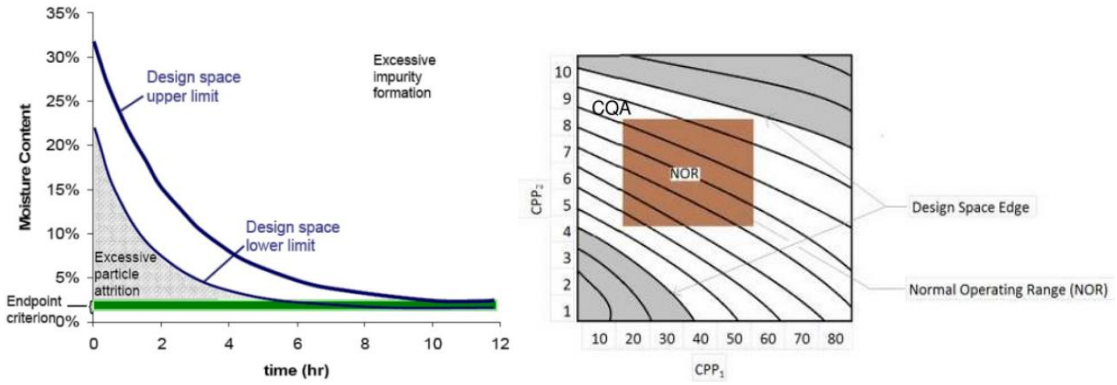


Figure 4: Knowledge space containing the Design space and NOR.

Quality is the degree to which a set of inherent properties of a product, system, or process fulfils requirements.

State of control is a condition in which the set of controls consistently provides assurance of continued process performance and product quality (Pharmaceutical Quality System - ICH Q10, 2011).

Capability of a process is the ability of a process to produce a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms.

2.3. Reasons to Validate Process / Regulatory Requirements

The cGMP regulations require that manufacturing processes be designed and controlled to guarantee that materials and finish product meet pre-determined quality requirements and do so consistently and reliably. This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

Nevertheless there are other reasons in addition to the regulatory requirements (cGMP regulations) for validating manufacturing processes. The dependence on intensive in-process and finished product testing can be reduced. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process will yield little scrap or rework, resulting in increased outputs. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also, when needed, the validation files contain data to support improvements in the process or the development of the next generation of the process (FDA, 2009).

2.4. Manufacturing Process Validation over Products Lifecycle

Several factors, such as manufacturing equipment, raw materials, and processing conditions, are likely to impact product quality. Assurance of product quality is derived from product and process design, adequate control of input process parameters, and testing of in-process and finished product samples. Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and process requirements.

A Process Validation is the collection and evaluation of data, from the process designed stage and continuing through commercial production, which ensure that the manufacturing process including equipment, building, personnel and materials is capable of achieving the intended results on a consistent and continuous basis (Guidance for Industry - Process Validation: General Principles and Practices, January 2011). In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program of a Pharmaceutical industry more effective and efficient. These practices should ensure uniform collection and assessment of information about the process and enhance the accessibility of such information later in the product lifecycle. Broadly speaking, any study that supports process-parameters ranges in the license application and/or master batch record is considered part of the process lifecycle validation study such as development, characterization, and process performance qualification (PPQ)(Process Lifecycle Validation: Applying Risk Management, 2013). This Guidance for Process Validation with this new approach (Guidance for Industry - Process Validation: General Principles and Practices, January 2011) describes process validation activities in three stages, that occur in more than one stage at the same time:

1. Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. The outcome is the design of a process suitable for routine manufacture that will consistently deliver product that meets its critical quality attributes.

2. Process Qualification: The process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

3. Continued Process Verification (CPV): Continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

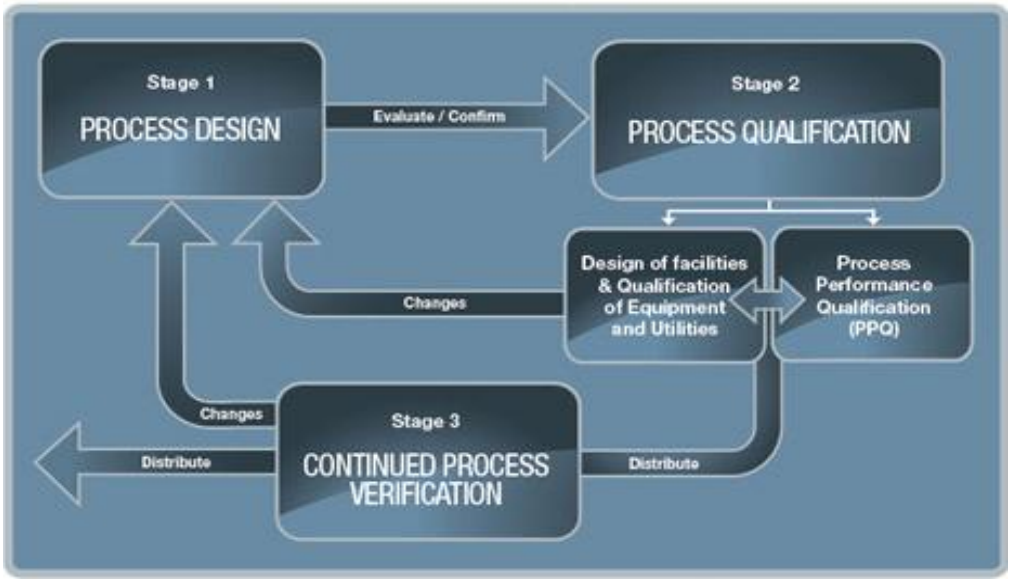


Figure 5: Process Validation – Life Cycle Approach
(FDA Process Validation Guidance and the PDA Process Validation Interest Group, March 14, 2012)

Process validation studies are expected to enhance process understanding/ knowledge throughout the product lifecycle. The manufactures are requested to follow ongoing programs to collect and analyze product and process data to evaluate the state of control of the process. With the issuance of the FDA guidance document on process-validation (Guidance for Industry - Process Validation: General Principles and Practices, January 2011), process validation activities should be viewed using a product lifecycle approach.

2.4.1. STAGE 1: Process Design

For pharmaceutical products under development, there are some basic rules that must be followed during transformation of an idea into a product to ensure patient protection: the product must be safe, product should be effective, and the product must meet a patient`s need or want.

PART 1 *– Building and Capturing Product and Process Knowledge/ Understanding*

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits (Guidance for Industry - Process Validation: General Principles and Practices, January 2011). Product realization can be defined as: “The sum total of all the processes that are used to bring a product into being” and involves starting with raw materials and working them into defined finish product (Process Lifecycle Validation: Applying Risk Management, 2013).

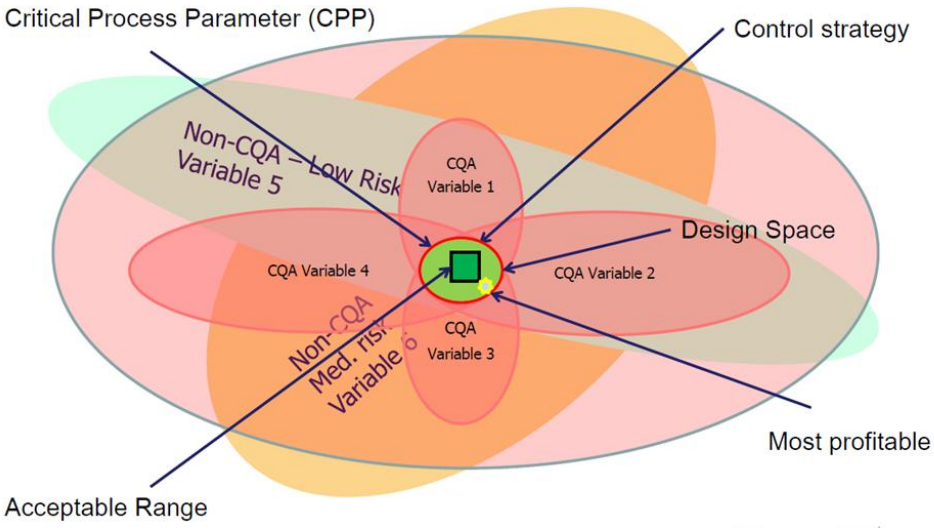


Figure 6: A Process design approach incorporating Quality by Design
(Quality by Design, 2012)

The aim of this stage is to design a process (e.g., process development, scale-up, and characterization) suitable for routine commercial manufacturing that can consistently deliver a product within specifications. In order to assure Product validation Lifecycle Quality by Design is the start concept of Process Design. Design space can illustrate understanding of parameter interactions and provides manufacturing flexibility. A good planning Process Development Project accomplishes the following tasks:

- Understand the process;
    - Assessment of CQAs;
    - Design Space (and Proven Acceptable Range);
    - Analysis of Critical Control Parameters (CCP) (or also called CPP) in order to ensure that the process will be under control;
- Develop a control Plan;
- Scale-up;
- Process Validation.

Very recently (in last October 2013) FDA and EMA announced their reflection on the topic of *Design Space Verification*. Design space verification is a demonstration that the proposed combination of process parameters and materials attributes is capable of manufacturing a quality product at commercial scale. Thus, Design Space Verification should occur over the product lifecycle as initial design space is normally developed based on experiments conducted at laboratory or pilot scale and often occurs solely at or near the target operating ranges. However, movements from one area to another area (e.g. scale-up) within the design space but re-establishing NOR in an unverified area, may pose higher risks or unknown risks due to potential models and assumptions (**Figure 6**). It is essential that these risks are understood and evaluate utilizing an appropriate control strategy, including but not restricted to the controls submitted in the dossier.

At this stage the activities and attributes that will be reflected in Master Batch Records and control records are designed. Product development activities provide key characteristics:

- Quality target product profile (Guidance for Industry - Q8 Pharmaceutical Development, May 2006);
- Intended dosage form;
- Route of administration;
- Expected drug product quality attributes based on knowledge management and risk management (Pharmaceutical Quality System - ICH Q10, 2011);
- General manufacturing pathway.

The basis for design of a pharmaceutical product is the quality target product profile (QTPP) defined as: "A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product". The QTPP forms the basis of design for development of the product and the process and should be one of the first documents to be placed in a product specification or design-history file (Process Lifecycle Validation: Applying Risk Management, 2013).

Designing an efficient process with an effective process control approach is dependent on process knowledge and understanding obtained. Therefore, product and process characterization activities are crucial:

– Design of Experiments (DOE) (Design space / Design Control, revealing multivariate interactions, relationships between CPPs and inputs, and CQAs and outputs). The results of DOE studies can provide an explanation for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes.

Figure 7: A quality by design approach to product and process development
(Quality by design study: An integrated multivariate approach to drug product and process development, 2009)

– Risk Assessments are used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained (see *Section 2.5.1 - Risk Assessment*). Risk-based approaches could be used to determine study type (e.g., generic or product specific), number of experiments, and scale. Risk-based study design shows how to incorporate prior knowledge and potential product quality risks in deciding process parameters (and identifying CPPs).

– Lab or pilot scale experiments assist in evaluation of certain conditions and prediction of performance of the commercial process.

– Computer modelling of certain unit operations or dynamics can provide process understanding and help avoiding problems at commercial scale.

The functionality and limitations of industrial manufacturing equipment should be considered in the process design, as well as predicted contributions to variability posed by different raw-materials lots, production operators, environmental conditions, and measurement systems in the production setting. It is crucial that activities and studies resulting in process understanding be reported. This information is useful during process qualification and continued process verification stages, including when the design is revised or the strategy for control is improved or changed (Guidance for Industry - Process Validation: General Principles and Practices, January 2011). The process is finalized prior to Process Validation batches at commercial scale.

PART 2 *– Establish Process Control Strategy*

FDA expects controls to include both examination materials quality and equipment monitoring. Particular attention is required to control the process through operational limits and in-process monitoring is essential in two scenarios:

1. When the product attribute is no measurable due to limitations of sampling or detectability (e.g., microbial contamination), or
2. When intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.

Process controls address variability to assure quality of the product. Controls can consist of material analyses and equipment monitoring at specific processing points Strategies for Process can be designed in different ways (See Section 2.6 - *Products' risk framework as part of Manufacturing* Process Validation):

- Reduce input variation;
- Adjust for input variation during manufacturing;
- Combination of both.

Process Analytical Technology (PAT) is an advanced control strategy that can include timely analyses and control loops to adjust the processing conditions so that the output remains constant.

2.4.1.1. *Technology Transfer – Lifecycle stage goal*

The purpose of technology-transfer activities is to transfer product and process knowledge between development and manufacturing and within or between manufacturing sites to achieve product realization. The transfer must demonstrate comparability of the product and process between the donor and recipient sites. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement (Pharmaceutical Quality System - ICH Q10, 2011).

There may be multiple quality risk assessments associated with a technology transfer (e.g., risk assessments for process changes, facility and equipment changes, method transfer, and multiproduct operations). It is important, therefore, that Quality Risk Management (QRM) activities are adequately planned and documented. This risk assessment should be performed during the introduction of a new product to assess and review any potential cross-contamination or non-routine risks of mix-up between existing products at the facility and the new product.

2.4.2. STAGE 2: Process Qualification

PART 1 *– Utility and Equipment Qualification*

During this stage it is demonstrated that utilities (**Figure 8**) and equipment are suitable for their intended use and perform their work properly. The following activities necessarily precede manufacturing products at the commercial scale:

- Installation Qualification (IQ);
- Operational Qualification (OQ);
- Performance Qualification (PQ).

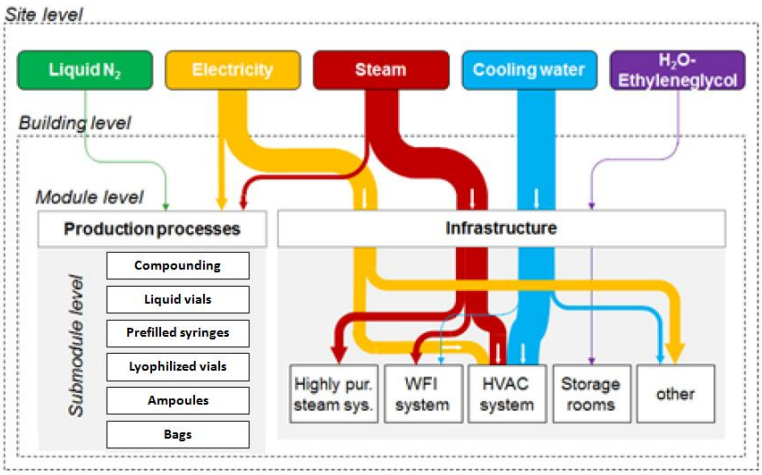


Figure 8: Some common utilities used in Hikma plants
(Applying Process Systems Engineering for Continuos Improvement in Pharmaceutical Production, 2013)

However these qualifications will not describe manufacturing processes, there are many other inputs associated with every unit operation.

Equipment and supporting systems to be used for PPQ need to be qualified in accordance to GMPs (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

PART 2 *– Process Performance Qualification (PPQ)*

The purpose of *process* performance *qualification* is to rigorously test the process to determine whether if it is capable of consistently producing an output or in-process or finished product which meets specifications. This stage has traditionally been known as “conformance runs” or “demonstration batches” or also called “process validation batches. In entering the process performance qualification phase of validation, it is understood that the:

- product, primary packaging, and process specifications have been established, documented, and essentially proven acceptable through engineering, laboratory data, pilot studies or other verification methods; and
- process and auxiliary equipment and the environment have been judged acceptable on the basis of installation and operation qualification studies.

A manufacturer is required to successfully complete PPQ before starting commercial distribution of drug product (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

The approach to PPQ should be based on:

1) Overall product and process understanding

Data should be analyzed to determine the normal range of variation for the process output. Knowing the normal variation of the output is crucial to determine whether if a process is operating in a state of control and if it is capable of consistently producing the specified output.

2) Demonstration of control / assess products risk framework

Process and product data should also be analyzed to identify any variation due to controllable causes. Depending on the nature of the process and its sensitivity, controllable causes of variation may include:

- Temperature;
- Presence of oxygen;
- Light;
- Humidity;
- Environmental contaminants;
- Inadequate employee training; and others.

The risk associated to causes of variation should be evaluated and appropriate measures should be taken to eliminate or control these controllable causes of variation. For example, extreme variations in temperature can be eliminated by installing heating and cooling system. Operators training can be improved and conducted more frequently and employees can be monitored more closely to assure that they are properly performing the process. Eliminating controllable causes of variation will reduce variation in the process output and result in a higher degree of assurance that the output will consistently meet specifications (FDA, 2009).

After routine production begins, data derived from monitoring the process and output product can be analyzed for variation and compared to the normal range of variation. Such analyses can detect when the process output is shifting so that corrections can be made before (Section 2.4.3 - *Stage 3: Continued Process Verification (CPV)*), or soon after, nonconforming product is produced.

3) Use of objective measures (statistics) to provide assurance of control

Successful PPQ is reflected by the level of robustness of the manufacturing formula, process recipe, and standard operating procedures (SOPs). This robustness can be given by statistical confidence. On the other hand statistical tools can support and facilitate quality risk management. They can provide effective data assessment, aid in determining the significance of the data set, and facilitate more reliable decision making (Guidance for Industry - Q9 Quality Risk Management, June 2006). For e.g. robustness of contamination controls that prevent presence of bioburden, endotoxin, or foreign contaminants in the aseptic process streams must be demonstrated in PPQ batches. This demonstration is accomplished through a combination of process controls such as raw material specifications and testing, equipment cleaning, and sanitization, facility/environmental requirements and controls, operational controls, and in-process monitoring during the production of the drug product. Regulators consider aseptic processing operations, such as sterile sampling, filtration, filling and lyophilization, to be high-risk processes.

4) Effects of scale understanding

Data must exist to demonstrate that commercial-scale manufacturing process is reproducible, can be maintained within established parameters, and consistently produces product that meets product specifications.

However, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data. Previous credible experience with sufficiently similar products and processes can also be supportive.

In most of the cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than during routine commercial production (see **Figure 9**). The level of scrutiny, testing, and sampling should continue through the process verification stage (Section 2.4.3 - *Stage 3: Continued Process Verification (CPV)*) as appropriate, to establish levels and frequency of routine sampling and monitoring for the particular product and process.

How many Validation Runs is State-of-Art today?

For many years the "magical three validation runs" completed successfully were regarded as state-of-the-art in order to be able to define a process as validated. But already in the PIC/S (Pharmaceutical inspection convention / Pharmaceutical inspection co-operation scheme - PIC/S, 25 September2007) on the topic qualification/ validation is stated analogously that theoretically the number of validation runs should be sufficient to show the normal level of variations and to recognize trends and to collect sufficient data for the assessment. But nevertheless the number three is still mentioned in this document.

In the new Guidance on Process Validation (Guidance for Industry - Process Validation: General Principles and Practices, January 2011) continues with these reflections and does not mention a number of validation runs any more. Instead the following considerations are made:

- For the duration of the heightened sampling and monitoring period the following should be considered:
    - Volume of production;
    - Process complexity;
    - Manufacturing Process Risk Analysis;
    - Level of process understanding;
    - Experience with similar products and processes.
- More variability implies more runs (to assure that the results are meaningful and consistent).
- More uncertainty implies more runs (to assure that the results are meaningful and consistent).
- Range of conditions allowed in written standard operating procedures.

Historically, also there has been limited application of risk assessment in defining the number of batches and studies. Under the concept of using a science- and risk-based approach, when selecting the number of batches in the PPQ, appropriate use of scientific data,

risk management, and statistical tools should be considered. Batches should not be selected without taking these considerations into account (Process Lifecycle Validation: Applying Risk Management, 2013).

Nevertheless, it seems that the one time rule of thumb for running three verification batches is no longer so straightforward; it depends on the level of product and process knowledge the company has acquired from development studies.

A manufacturing process that uses PAT[2] may follow a different PPQ approach. Stage 1 and Stage 2 of this Lifecycle Process Validation approach should focus on the measurement system and control loop for the measured attribute. Regardless, the objective of validating any manufacturing process is the same: *establish scientific evidence that the process is reproducible and will consistently deliver quality products.*

Product Performance Qualification

The purpose of *product* performance qualification is to demonstrate that the process has not adversely affected the finished product and that the product meets its predetermined specifications and quality attributes. Product performance qualification and design validation of initial finished product are directly related. According to the design control requirements, design validation shall be performed under defined operating conditions on initial production units, engineering batches, or Process Validation batches. Products used for design validation should be manufactured using the same production equipment, methods and procedures in order to challenge commercial production. Otherwise, the product used for design validation may not be representative of production units and cannot be used as evidence that the manufacturing process will produce a product that meets pre-determined specifications and quality attributes.

PPQ Documentation

Any planned, documented study that adds process knowledge and supports product licensure is considered part of process validation. Risk-based approaches could be used to determine study type (e.g. generic or product specific), number of tests and scale (Process Lifecycle Validation: Applying Risk Management, 2013). Procedures for monitoring and control of process parameters must be established and maintained for validated processes. A PPQ Protocol and subsequent PPQ Report are the main documents and the guidelines of each validated process.

[2] PAT processes are designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop o the process maintains the desired quality of the output material.

a) PPQ Protocol

Process Performance Qualification Protocol is a written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results. Thus, this plan should document a complete list of process validation studies required for product/ process licensure, including the appropriate level of effort and timing of process validation activities. Understanding challenges in applying risk management and common factors that may result in unsuccessful process validation would help to take the suitable measures to overcome them (Process Lifecycle Validation: Applying Risk Management, 2013). Planning for the validation must include the following main elements as well as any other relevant issues that must be addressed to conduct the validation study:

- Manufacturing conditions, including operating parameters, processing limits, conditions to be placed on preceding processes and components inputs.
    - Consideration of maintenance and repairs needs;
    - Assumptions (shifts, operators, equipment, components);
    - Identification of equipment to be used in the process;
    - Identification of utilities for the process equipment and quality of the utilities.
- Criteria and process performance indicators[3] that allow a decision based on science and risk about the ability of the process to consistently produce quality products.
    - Product risk analysis – assessment process and product risk framework;
    - Process parameters and Product characteristics to be controlled and monitored, and methods for controlling and monitoring;
    - Statistical methods for data collection and analysis;
    - Provision for addressing deviations from expected conditions and handling of nonconforming data. Data cannot be excluded from further consideration in terms of PPQ without a documented, scientific justification.
- Testing, including acceptance criteria.
- Data collection and evaluation.
- Sampling plan (intra- and inter-batch quality) including sampling points, number of samples, and frequency of sampling for each unit operation and attribute. The confidence level selected is based on *Risk Analysis* as it relates to the particular

[3] **Performance indicators:** Measurable values used to qualify quality objectives to reflect the performance of an organization, process or system, also known as performance metrics in some regions(Pharmaceutical Quality System - ICH Q10, 2011).

attribute under examination. Sampling during this stage should be more extensive than is typical during routine production (see **Figure 9**).

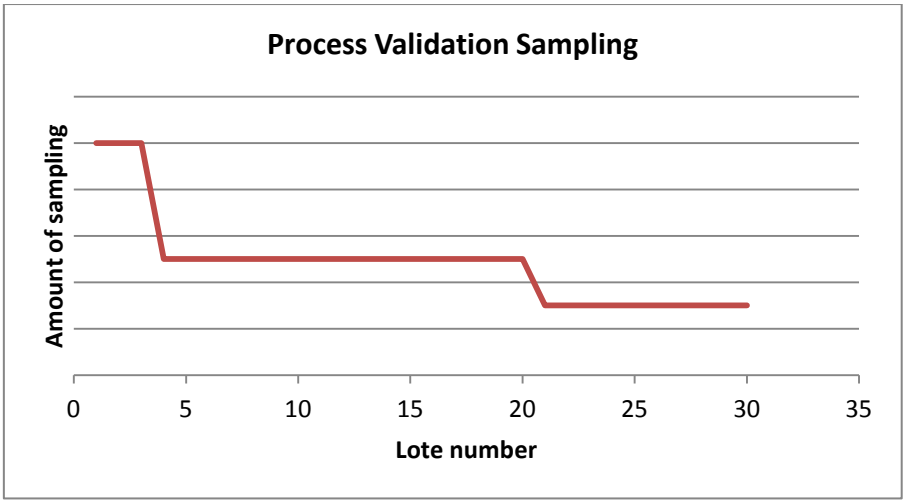


Figure 9: Scheme exemplifying Process Validation Sampling over Product Lifecycle

The validation plan should also cover the installation and operation qualification of any equipment used in the process performance qualification, and product performance qualification (FDA, 2009). Proper training and motivation of personnel are prerequisites to successful validation. The revision and approval of the protocol by appropriate departments and the quality unit are necessary prior to its execution. The commercial manufacturing process and routine procedures must be followed during PPQ Protocol execution (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

b) PPQ Report

A report is prepared in a timely manner after the completion of PPQ runs documenting and assessing adherence to the written PPQ Protocol (**Figure 10**). This report is supposed to:

- Discuss and cross-reference all aspects of the protocol;
- Summarize data and results from PPQ runs;
- Evaluate any unexpected observations and additional data not specified in the PPQ protocol;
- Summarize and discuss all manufacturing non-conformities such as deviations, aberrant test results, or other information that has bearing on the validity of the process;
- Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls;

- Conditions that may indicate that the process or part of the process should be revalidated;
- State a clear conclusion regarding state of control;
- Include all related department and quality unit in the review and approval.

Release of PPQ Batches

Normally, completion of all PPQ batches and approval of PPQ reports is required for commercial distribution of a product and a high degree of assurance in the process achieved. Though, under special circumstances, concurrent release[4] of PPQ batches may be acceptable:

- Infrequently manufactured (orphan drugs);
- Short half lives (shelf life);
- Drug shortage.

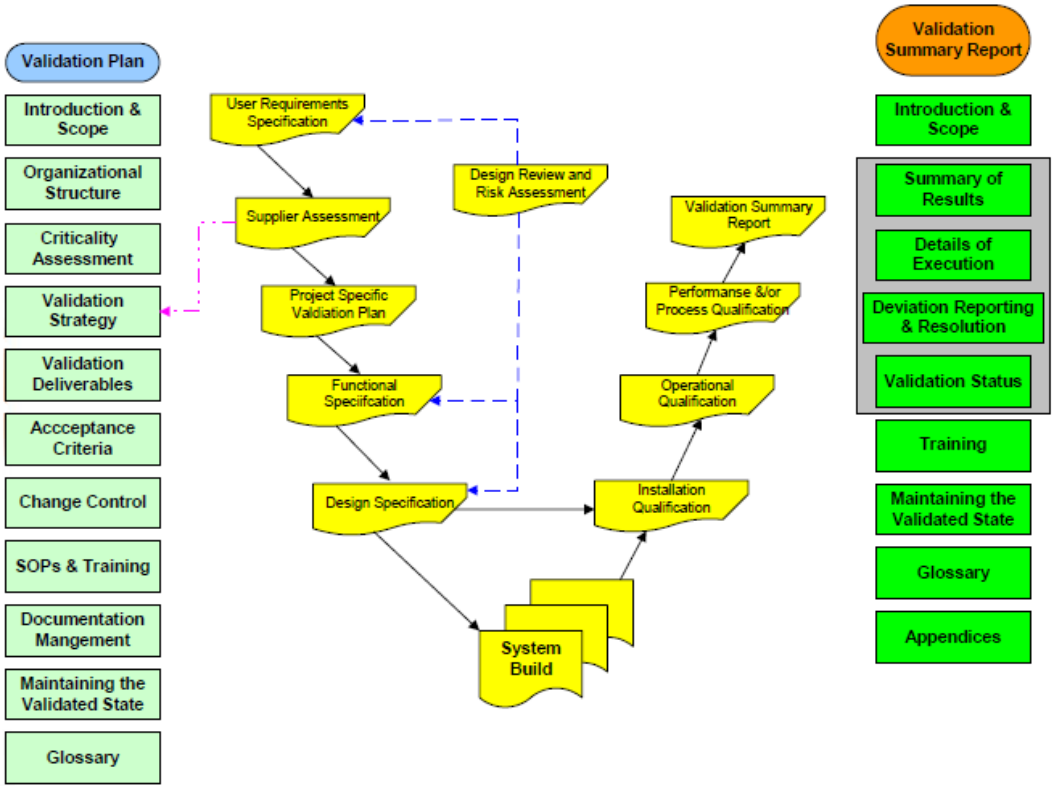


Figure 10: Risk-Based Validation Lifecycle
(Risk-Based Validation and Requalification of Process & Equipment, 2009).

4 **Concurrent release:** Releasing for distribution a lot of finish product, manufactured following a qualification protocol, that meets the lot release criteria established in the Protocol, but before the entire study protocol has been executed.

2.4.3. Stage 3: Continued Process Verification (CPV)

Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes (Guidance for Industry - Process Validation: General Principles and Practices, January 2011). Various changes that occur during a manufacturing process lifetime include normal process variability over time (see *Section 4.3.2 - Controlled Variation),* changes in the manufacturing equipment that influence the process and control system, and process improvement. Trending of process monitoring data at established intervals is useful in the ongoing evaluation of the process. Statistical analysis and trending of the data should be applied to alert any undesirable process behavior (see *Chapter 4* - PARAMETERS AND METHODS – Quality Risk Management Tools). Where no significant changes have been made and process-monitoring verification confirms that slight changes have not impacted the system or process and maintained consistent results, there is then no need for repletion of PPQ runs. Certain regulatory authorities may require revalidation for a specific product or process. Changes to processes, raw materials, specifications, methods, procedures, labeling, and packaging systems must be evaluated per approved change-control procedure. Hence, lifecycle approach for process validation is now an expectation from regulatory agencies (Guidance for Industry - Process Validation: General Principles and Practices, January 2011) (Guideline on Process Validation, 29 March 2012).

How is Continued Process Verification accomplished?

Consistency beyond the initial qualification batches is demonstrated through continuing monitoring of a subset of the original parameters evaluated. In order to accomplish it the following proceedings is recommended (refer to **Figure 11**):

- System for detecting unplanned divergence from the process as designed;
- Ongoing program to collect and analyze product and process data that relate to product quality (process trends, in-process controls, finished product testing against specifications);
- Statistical trending reviewed by trained personal (see **Figure 12** and **Figure 13**);
- Ongoing process monitoring of process parameters and quality attributes;
- Annual Product Quality Reviews (PQR);
- Executed batch records; Management review and production staff feedback
- CAPAs;
- Ongoing risk management;
- Improvement initiatives through process experience;
- Other means to detect variation (deviations / non-conformances, out-of-specification results, out of trend results, batch records, defect complaints, adverse event reports, process yield variation etc.).

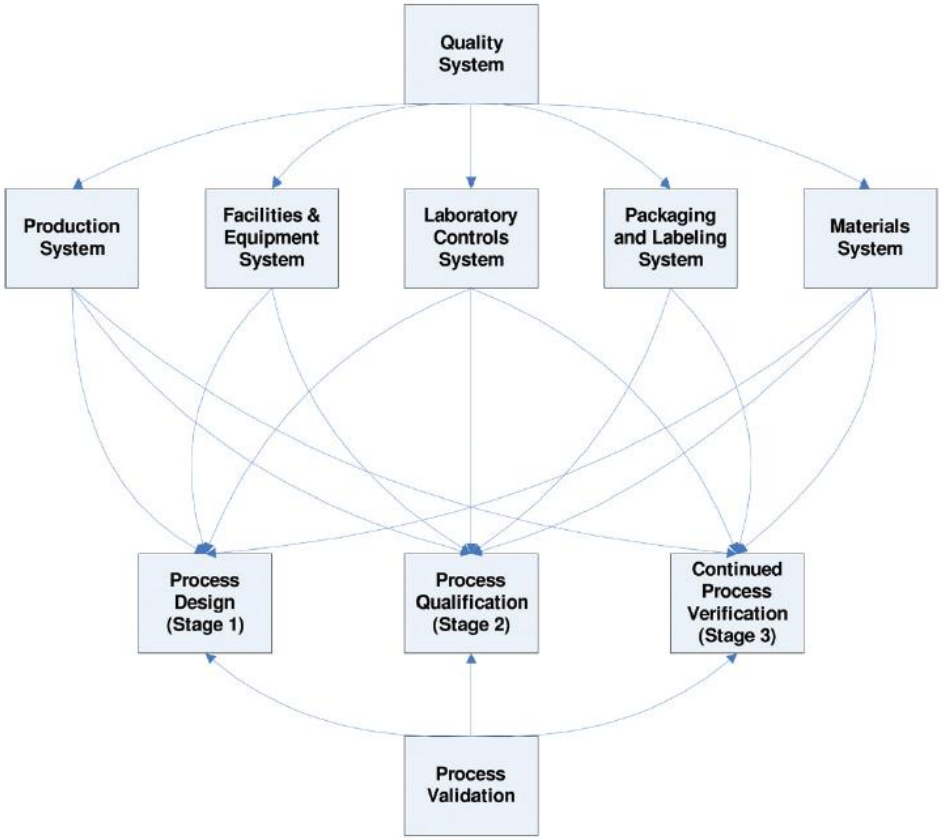


Figure 11: Quality system Hierarchy

FDA recommends continued monitoring and sampling of process parameters and quality attributes at the level established during PPQ until sufficient data is available to generate variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. These activities might suggest ways to improve and optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics.

Sampling frequency can then be adjusted to a statistically appropriate and representative level. The monitoring strategy should be documented (e.g., parameter monitoring, and statistical process control) (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

In contrast, a science- and risk-based approach applied through the process lifecycle is more effective and robust. The evaluation of process changes can determine the significance of the change and define the necessary supporting validation study requirements and any potential requirements for regulatory reporting. An evaluation of the potential impact of a change on that unit operation, as well as potentially impacted steps downstream of that unit operation, is required to determine the scope and significance of required verification studies. It is important to determine the significance of a process change and define the review schedule of a validated process (Process Lifecycle Validation: Applying Risk Management, 2013).

2.4.3.1 Applying New Guidance to Old Products

The ambition of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. *In Theory* manufacturing experience should yield increased knowledge and process improvements, and a lack of process improvements indicates lack of process understanding and failure to learn (implement learning).

In practice, if it is not broken, it is not fixed! Before, the manufacturers were reluctant to change a process once validated and to look backward at released lots. Analysis, trending, and assessing variability are the basis for the identification of critical process parameter (CPPs) and critical material attributes (CMAs) for specific unit operation or process step needs to be evaluated according to 2011 FDA Process validation Guidance. Not only deviations or OOS results are the impulse needed for the change. A proactive search for controlling CPPs and CMAs is the new challenge requested from authorities. The initial selection of parameters or evaluation in process studies should include scientific rational and the use of risk-based approaches where relevant. The highest risk (i.e. parameters with the greatest likelihood of product impact) should be evaluated first.

2.4.3.2 Establishing a CPV Program

Several possible methods of organizing CPV are available, one of which is assembling a multi-disciplinary team. For this purpose, the management appoints a person responsible for process validation (process validation officer), who must have adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and capability.

A validation program (SOP or Validation Plan), which determines the scope of its work, its priorities, the time-schedule, the resources needed, etc. should be approved across all departments and functions concerned. The basis of the program should also be well established concerning data collection and recording, plotting, analyses, response to out-of-control (OOC) results, reporting frequency and pathway for improvements.

After CPV program approval small steps can be given for assess normality of data and establish control limits data points needed, once again the first evaluated should be the highest risk. The data can be obtained, either retrospectively or prospectively, plot data within specification limits, look for obvious issues as trends (**Figure 12**), visual mean value offset from target or specification centerline or bi-modal results (**Figure 13**) or insufficient resolution (pH only recorded to 0.1 unit), or other specificities in process outputs.

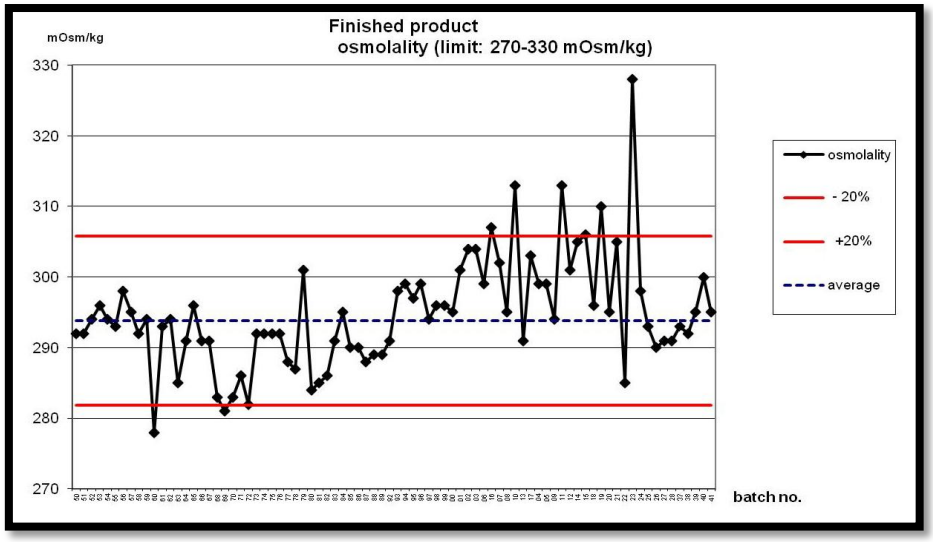


Figure 12: Challenges: Artefacts are found in data review – Trend.

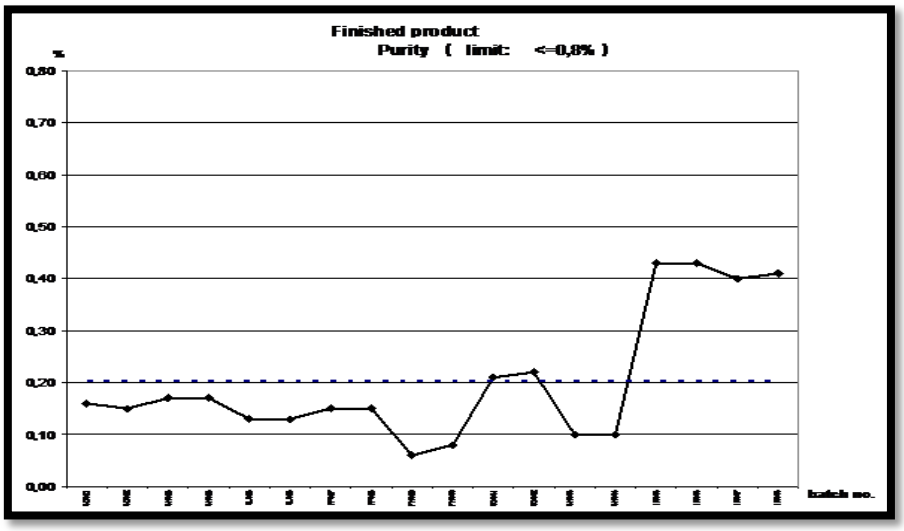


Figure 13: Challenges: Artefacts are found in data review – Bimodal results.

2.5. Connection of Process Validation, Quality System and Quality Risk Management

Before any batch is commercialized, the manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce drug products meeting those attributes relating to identity, strength, quality, purity, and potency (CQAs). The assurance should be obtained from objective information and data from laboratory, pilot, and/or commercial scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

Figure 14: Diagram of the ICH Q10 Pharmaceutical Quality System Model (Pharmaceutical Quality System - ICH Q10, 2011)

The Pharmaceutical Quality System (PQS) defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications. As described earlier, a successful process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is appropriate for its intended use. This principle incorporates the understanding that the following conditions exist:

- QUALITY, SAFETY and EFFICACY are built into the product.
- Quality cannot be adequately assured merely by in-process and finish-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finish product meets all quality attributes including all specifications (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

PQS continual improvement approach (**Table 1**) compiles essential elements as, monitoring of process performance, CAPA, Change management; supportive elements to identify and implement appropriate product quality improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently (Pharmaceutical Quality System - ICH Q10, 2011).

The benefits of QRM include early detection of risks, providing a broader reach than traditional Quality Assurance and Quality Control methods can obtain and performing deeper insights with regards to quality risks and compliance around clinical development processes within an organization. The core objectives for effective quality risk management will help to

ensure patient safety and data integrity. Both EMA and FDA have been active in fostering these concepts.

There is a variety of potential uses for quality risk management tools and principles in the injectables manufacturing (Integrated Quality Management, Regulatory Operations, Development, Facilities, Equipment and Utilities, Materials Management, Production, Laboratory Control, Stability Studies, Packaging and Labelling). The focus of the QRM tools in the next chapters will be emphasizing the use for manufacturing process validation of Injectables.

Quality risk management (QRM) is integral to an effective PQS, as it is the cornerstone of any science- and risk-based approach for modern drug development and manufacturing (Brindle, et al., 2012). It can provide a proactive approach identifying and prioritising, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. QRM help setting meaningful specifications and CPPs to ensure product CQAs are met (Pharmaceutical Quality System - ICH Q10, 2011).

QRM is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. A model for QRM according to Q9 guidance is outlined in the diagram (**Figure 15**).

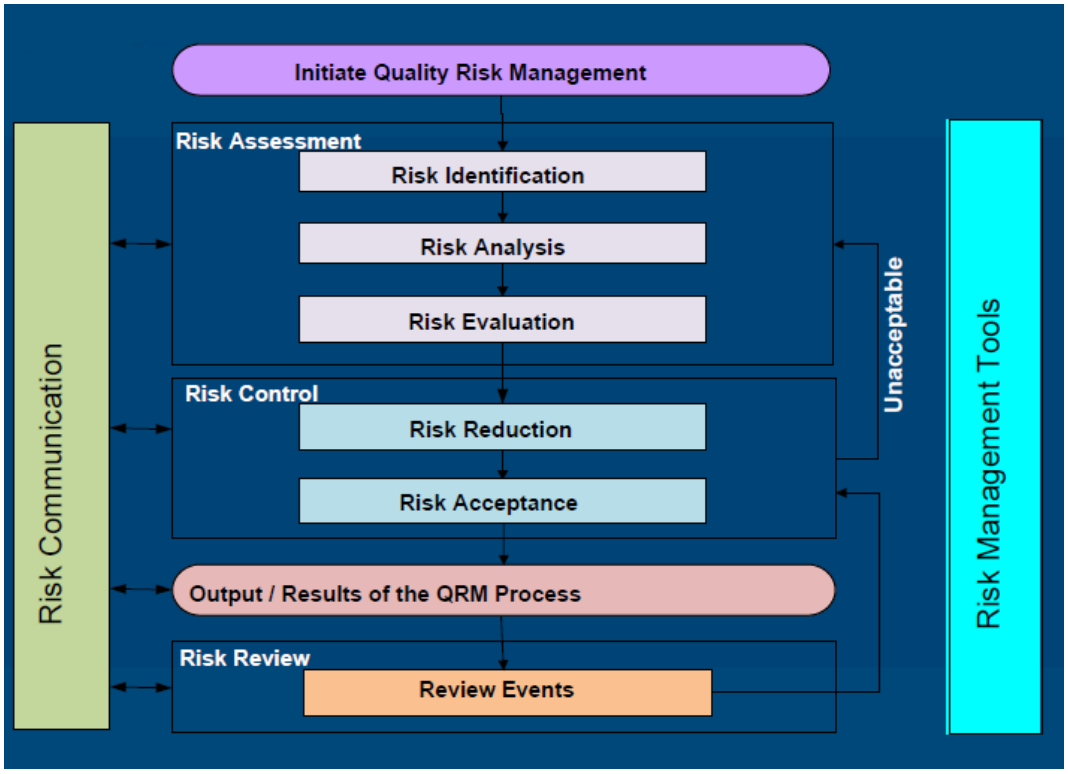


Figure 15: Overview of a typical quality management process
(Guidance for Industry - Q9 Quality Risk Management, June 2006).

2.5.1. Risk Assessment

An appropriate risk assessment can minimize the process risk. The risk assessment has to be part of a quality risk management system (**Figure 15**), which should include experts from multiple disciplines to ask the following questions:

- What can go wrong in the process?
- How frequently occurs?
- What are the consequences if this process goes wrong?

The first step of risk assessment construction is RISK IDENTIFICATION. This first task is identifying the hazards (e.g. illustrated in **Figure 16**). Essentially, identifying the hazards answers the questions, "What can go wrong?"; "What can cause the problems?". This is a brainstorming activity as important part of this thesis. This activity should generate many known and potential failure modes. The goal is to make this list as exhaustive as possible. Since identifying all potential failures can be an enormous task when considering an entire manufacturing process, the process map generated during the initiation phase of the risk management process is a valuable tool to generate the logical breaks that organize and focus the brainstorming (Validation & Complience: Using Risk Analysis in Process Validation, 2007).

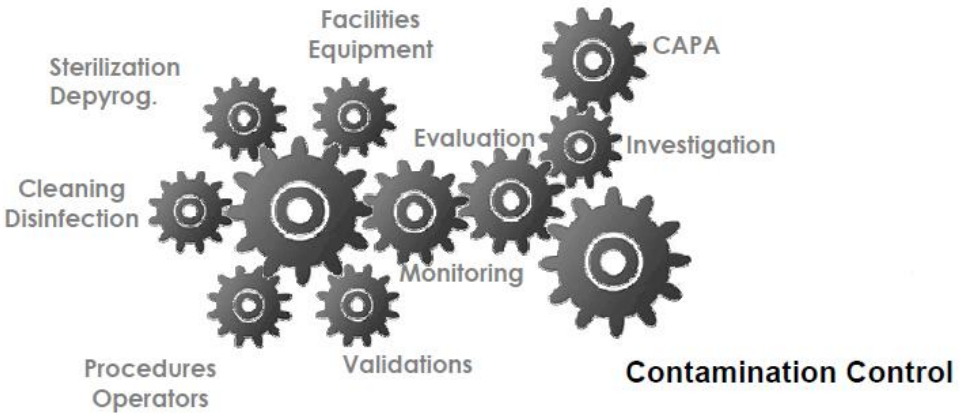


Figure 16: Sterility as CQA of an injectable product and sources of variability that should be controlled.

The next step in the risk assessment phase is risk analysis. RISK ANALYSIS involves using the actual *risk assessment tool*. The qualitative or quantitative estimation of severity or the consequence, and the likelihood and the ability to detect the failure, are determined during the risk analysis (Guidance for Industry - Q9 Quality Risk Management, June 2006). At this stage, for each identified risk the probability of occurrence (O), the Severity of the risk (S) and Detectability (D).

The final step in the risk assessment is the RISK EVALUATION. The risk evaluation is the gap analysis of the calculated risk relative to the acceptable level of risk (the action threshold). At this point, the risk assessment phase ends.

The risk management process would continue through the steps of risk control, risk review and communication (**Figure 15**). This implies that over the course of the product`s lifecycle, the risk assessment is reviewed. This review includes adjustments to regulatory requirements or to additional information related to the new process.

2.5.2. Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level and increase detectability. The efforts used to control the potential risk control should be proportional to the significance risk level(Guidance for Industry - Q9 Quality Risk Management, June 2006).

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see **Figure 15**). Risk reduction might include actions taken to mitigate the severity and probability of damage. Processes that improve the detectability of hazard and quality risks might also be used as part of a risk control approach. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk (decided case by case assessment). Risk acceptance can be a formal decision to accept the minor risk or it can be a passive decision in which minor risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk (e.g. illustrated in green bar in **Figure 17**). In these circumstances, it might be necessary an appropriate quality risk management support and that quality risk is reduced to a specified (acceptable) level.

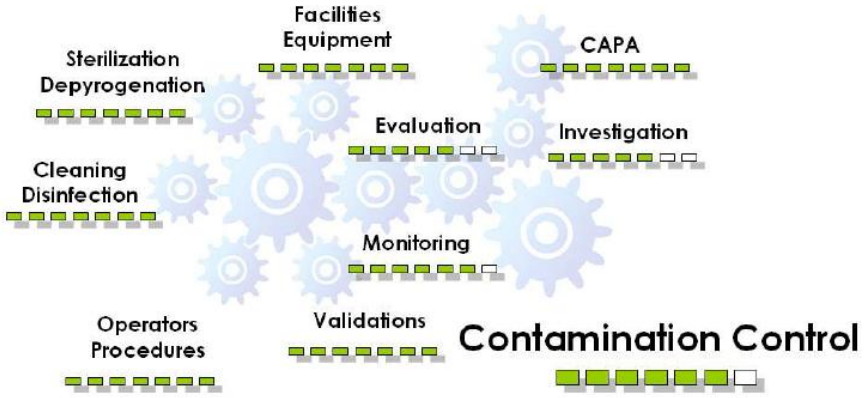


Figure 17: Aseptic process using a risk-based approach - contamination control.

2.5.3. Risk Review

Address the need to revisit the risk assessment to take into account any new information/ experience (Quality Risk Management - The Pharmaceutical Experience, 2011):

- Determine an appropriate frequency
- Purpose – what items will be reviewed

2.5.4. Risk Communication

A product production is efficiently controlled when the information is spread across all departments involved:

- Communicating information with the key groups;
- Communicating information with stakeholders throughout;
- Understanding our risks and conveying them to others (Quality Risk Management - The Pharmaceutical Experience, 2011).

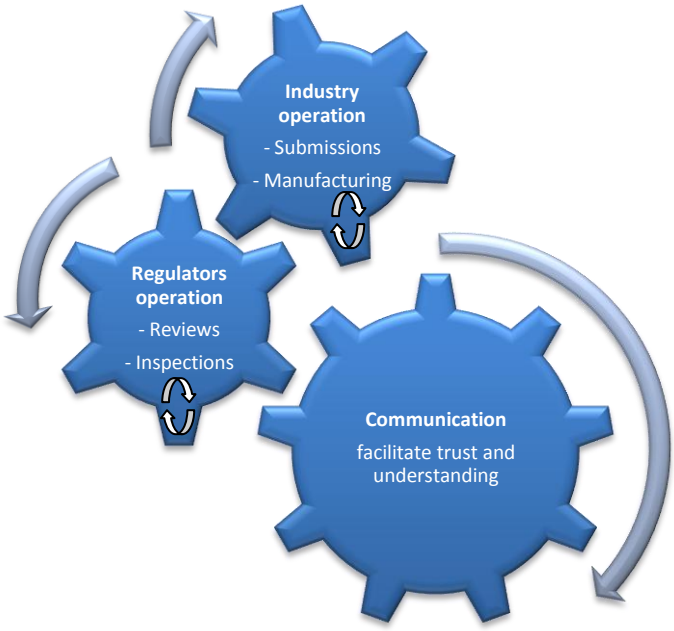


Figure 18: Systems of a Quality Risk Management

The information obtained from the risk analysis will only be useful if the input is appropriate. The results from the risk assessment often dictate the number of unit operation steps needed to reduce specific risks to acceptable levels.

2.6. Products' risk framework as part of Manufacturing Process Validation

A successful validation program depends upon information and knowledge from product and process development that pharmaceutical manufactures hold. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes (Guidance for Industry - Process Validation: General Principles and Practices, January 2011). Validation is therefore essential as it ensure the production of a safe product that minimizes the risk to patients. Risk analysis in process validation promises to minimize process risk. Risk-assessment tools help to define the process and identify crucial areas and/or steps in that process, areas of risk and/ or hazard, and critical control points (Jain, et al., 2011).

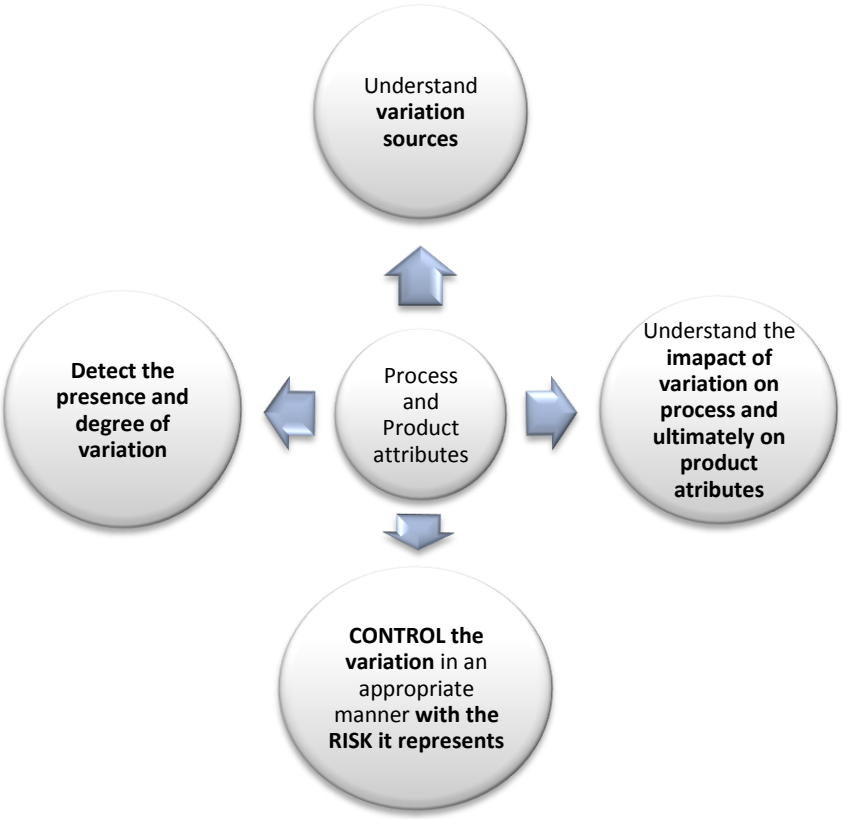


Figure 19: Schema for Identification and Control of variations in manufacturing process and product quality (Guidance for Industry - Process Validation: General Principles and Practices, January 2011)

The manufacturer should judge the degree of quality assurance on its own manufacturing process to justify commercial distribution of the product. Qualification efforts in addition to manufacturing process understanding and associated variations controlled will lead to adequate assurance of quality (**Figure 19**). After process established and confirmed, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.

Summing up, QRM can be part of Validation to:

- Identify the scope and extent of verification, qualification, and validation activities (e.g. analytical methods, processes, equipment, and cleaning methods);
- Determine the extent for follow-up activities (e.g., sampling, monitoring, and re-validation);
- Distinguish between critical and noncritical process steps to facilitate design of a validation study.

Risk-Based Validation as part of a Robust Process

Robustness is the ability of a process to consistently produce the same product while remaining unaffected by small variations in the process. It is possible to have a repeatable process and not have a robustness process, but it is unlikely to have a robust process that is not repeatable.

One approach to evaluating robustness of a process is to evaluate critical process steps, critical analyses and critical product parameters (**Figure 16**). This evaluation is considered "most appropriate challenge" of the parameter limits. Another (more common) approach is to obtain information on challenge conditions during process development followed by PPQ.

The ranges of the critical process parameters and the controls must be defined. They may be defined either during process development or during process development.

Chapter 3 INJECTABLE PRODUCTS OVERVIEW

Parenteral medicines are prepared scrupulously by methods designed to ensure that they meet pharmacopeial requirements of sterility, pyrogens/ endotoxins, particulate matter and other contaminants. Parental preparations (solutions, emulsions, or suspensions) may contain one or more active ingredients, packaged in either single-dose or multi-dose containers. Parental preparations are intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they can contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or lesion. An injection is a preparation intended for parenteral administration and/or for constituting or diluting a parental article prior to administration (The United States Pharmacopeia, 2013).

3.1 Nomenclature and definitions

The following nomenclature pertains to five general types of preparations, all of which are suitable for, and intended for, parental administration. They may contain buffers, preservatives, or other added substances (The United States Pharmacopeia, 2013).

1. *[DRUG] Injection – Liquid preparations that are drug substances or solutions theoref.*
2. *[DRUG] for Injection – Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.*
3. *[DRUG] Injectable Emulsion – Liquid preparations of drug substances dissolved or dispersed in a suitable liquid medium.*
4. *[DRUG] Injectable Suspension – Liquid preparations of solid suspended in a suitable liquid medium.*
5. *[DRUG] for Injectable Suspension – Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.*

There are four main forms of parenteral preparations: injections, intravenous infusions (large volume parenterals), powders for injections, and implants. Certain injections and intravenous infusions may be presented in the form of sterile concentrated solutions, which must be suitably diluted before use (World Health Organization).

3.2 Vehicles and Added substances

The vehicles for aqueous injections meet requirements of the Pyrogen Test or the Bacterial Endotoxins Test, whichever is specified. Water for Injection generally is used as the vehicle, unless otherwise specified in the monograph. Sodium chloride may be added in amounts sufficient to render the resulting solution isotonic. Fixed oils used as vehicles for nonaqueous Injections are of vegetable origin, are odorless or nearly so, and have no odor suggesting rancidity (The United States Pharmacopeia, 2013).

Parenteral preparations may contain excipients such as solvents, suspending agents, buffering agents, substances to make the preparation isotonic with blood, stabilizers, or antimicrobial preservatives. The addition of excipients should be kept to a minimum. When excipients are used, they should not adversely affect the stability, bioavailability, safety, or efficacy of the active ingredient(s), or cause toxicity or undue local irritation. There must be no incompatibility between any of the components of the dosage form (World Health Organization) and there must be no interference with therapeutic efficacy or with the responses to the specified assays and tests (The United States Pharmacopeia, 2013). No coloring agent may be added, solely for the purpose of coloring the finished preparation, to a solution intended for parenteral administration. A suitable substance or mixture of substances to prevent growth of microorganisms must be added to the preparation intended for injection that are package in multiple-dose containers, regardless of the method of sterilization used, unless one of the following: (1) there are different directions in the individual monograph; (2) the substance contains a radionuclide with physical half-life of less than 24 hours; and (3) the active ingredients are themselves antimicrobial. Such substances are used in concentrations that will prevent the growth of or kill microorganism in the preparations for injection. The air in the container may be evacuated or be displaced by a chemically inert gas. Where specified in a monograph, information regarding sensitivity of the article to oxygen is to be provided in the labelling (The United States Pharmacopeia, 2013). The containers should be equipped to ensure adequate protection of the contents after partial withdrawal. In order to minimize the risk of contamination resulting from multiple penetrations of the closure, the contents of a multi-dose preparation should normally not exceed 30 ml (The United States Pharmacopeia, 2013).

3.3 Aseptic Manufacturing

The manufacturing process should meet the requirements of Good Manufacturing Practice. Also system of marketing authorisations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy (European Commission, December 2010).

Aseptic filling is an aseptic process that requires the close coordination and complex interaction between personal, sterilized product, the fill/finish equipment system, clean room and support facilities, and sterilized filling components (Comprehensive review on aseptic fill/finish manufacturing as per regulatory guidelines, 2011). The quality of starting materials, the design and maintenance of the equipment and the method of manufacture must be such as to ensure the stability of the active substance and the finished product which is sterile and free of pyrogens and particulate matter (The United States Pharmacopeia, 2013).

Aseptic manufacturing is used in cases, where the drug substance is instable against heat; hence sterilization in the final container closure system is not possible. Aseptic processing attracts a high level of regulatory scrutiny due to risks associated with this type of manufacturing and its potential adverse effect on the health care consumer (Comprehensive review on aseptic fill/finish manufacturing as per regulatory guidelines, 2011). From the clinical viewpoint all parenteral preparations must be pyrogen-free (The United States Pharmacopeia, 2013).

With respect to parental preparation sterility, the filling manufacturing process of a bulk solution is aseptic (following aseptic technique) and, in this case, the solution is filtered through a 0.2 µm filter or lower porosity filter (and procedures validated per media fill); or the product is terminally sterilized. For the sterilization of parenteral preparations heating in an autoclave is the method of choice for aqueous preparations and should therefore be used whenever possible.

When a parenteral preparation is liable to deterioration due to oxidation, the operation of filling may be performed in an atmosphere of suitable inert gas, such as nitrogen, whereby the air in the container is replaced by filtered (sterile) nitrogen.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during production of parenteral preparations should include monitoring of environmental conditions (especially with respect to particulate and microbial contamination), bacterial endotoxins, pH and clarity of solution, freedom from particulate matter, and integrity of container (absence of leakage, etc.). For dispersions controls should also include the particle size of the dispersed phase, and for powders for injections the uniformity of content and mass, moisture content, and the ease of reconstitution. The presence of preservatives or other additives should be determined as these can influence the choice of assay method (World Health Organization).

3.3.1 Visual inspection

Inspect the solutions, reconstituted solutions, and intravenous infusions (except dispersions). They should be clear and free from visible particulate matter.

3.3.2 Containers

Drug product, container, and closure are first subjected to sterilization methods separately and appropriately; which consists of several consecutive and necessary working steps, each of them contributing its part towards the aim of manufacturing an aseptic product (prevention of microbial contamination) (Comprehensive review on aseptic fill/finish manufacturing as per regulatory guidelines, 2011). Parenteral preparations are usually supplied in glass ampoules, bottles or vials, plastic bottles or bags, and prefilled syringes, which can be amber in the case of light-sensitive substances.

Except where otherwise indicated in individual monographs, these containers should be made from material that is sufficiently transparent to permit the visual inspection of the contents. They should not adversely affect the quality of the preparation, allow diffusion of any kind into or across the material of the container, or yield foreign substances into the preparation (The United States Pharmacopeia, 2013).

3.3.3 Closures

Closures for parenteral preparation containers should be equipped with a firm seal to prevent entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They should not be made of components that react with the contents, nor should they allow foreign substances to diffuse into the preparation. Plastic materials or elastomers of which the closure is composed should be sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles. Closures for multidose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

3.3.4 Labelling

Every pharmaceutical preparation must comply with the labeling requirements established under Good Manufacturing Practice. The label should include:

(1) the name of the pharmaceutical product;

(2) the name(s) of the active ingredient(s); INNs should be used wherever possible;

(3) the amount of the active ingredient(s) in a suitable dose volume and the volume in the container; for powder for injections: the amount of the active ingredient(s) in the container;

(4) the batch (lot) number assigned by the manufacturer;

(5) the expiry date and, when required, the date of manufacture;

(6) any special storage conditions or handling precautions that may be necessary;
(7) directions for use, warnings, and precautions that may be necessary; and
(8) the name and address of the manufacturer or the person responsible for placing the product on the market.

For parenteral preparations that are solutions or dispersions, the concentration of the active ingredient(s) should be given in terms of mass or biological activity per volume. For concentrated solutions, labels should state the composition and the dilution to be carried out before use.

3.4 Injections

Injections are sterile, pyrogen-free solutions or dispersions (emulsions or suspensions) of one or more active ingredients in a suitable vehicle.

3.4.1 Suspensions

A suspension drug product is typically aqueous-based formulations that contain therapeutically active ingredients and can also contain additional excipients. As the other injectable products, an aqueous-based suspension must be sterile. The final formulation should be expressed in concentration (i.e., amount per unit volume or weight), as well as amount per container (U.S. Department of Heath and Human Services and FDA and CDER, 2002).

The production of injectable suspensions involves a complex manufacturing process. Suspensions are mixtures of solids with liquids, gases with liquids, in which there is no dissolution but there is a dispersion of one substance in the other. Colloids are the most common form of a suspension, and are characterized by having a high amount of dispersed particles. This particles are normally at size > 0.1 µm.

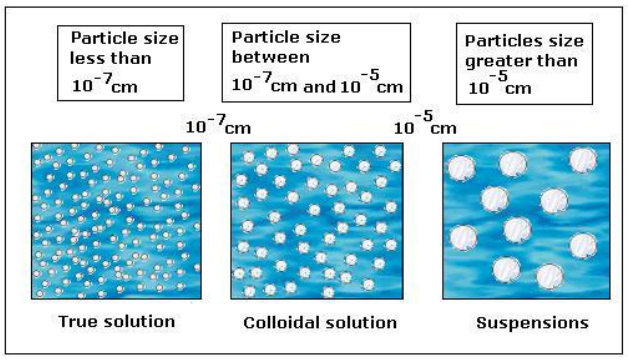


Figure 20: Differences in Particle sizes between a “True solution”, a Colloidal solution” and “Suspensions”.

The suspensions are heterogeneous systems, in which one substance is the disperse phase, distributed in small units in another substance that constitute the dispersant phase or continues phase.

The composition of suspension formulations may be crucial in defining the physical stability and the performance characteristics of the drug product. The density and suspension proprieties of the solid materials of the formulation and potential for agglomeration (**Figure 21**) should be considered. Therefore, this type of injectable product is very difficult to be manufactured and additional controls are necessary to the production process. Moreover, interaction of the suspended drug substance with the various internal container closure system components can also contribute to a non-homogeneous distribution of the drug product. This phenomena which may be exacerbated with time, can contribute to inconsistent particle size distribution and medication dose delivery.

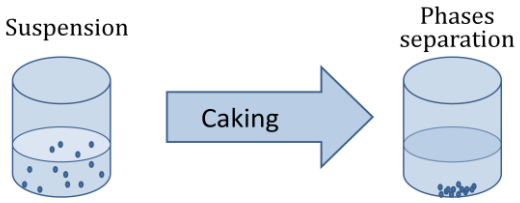


Figure 21: Suspension and the phenomenon of caking which shows that suspensions are thermodynamically instable systems.

3.5 Intravenous infusions

Intravenous infusions are sterile, pyrogen-free aqueous solutions or emulsions with water as continuous phase, usually prepared to be isotonic. They are intended for administration in large volumes (usually 100 ml or more), and should not contain any antimicrobial preservatives.

On visual inspection, emulsions for intravenous injection should show no evidence of phase separation. The particle size of the dispersed phase should be controlled by the manufacturer.

3.6 Implants

Implants are solid preparations containing one or more active ingredients. They are of a size and shape suitable for parenteral implantation, and provide release of the active ingredient(s) over an extended period of time. They are presented in individual sterile

containers. All requirements for these specialized dosage forms are given in the individual monographs.

3.7 Powders for injections

Powders for injections are solid substances (including lyophilized products), distributed in their final containers and which, when shaken with the prescribed volume of the appropriate sterile liquid, rapidly form either clear and practically particle-free solutions or uniform suspensions. Powders for injections, after dissolution or suspension, comply with the requirements for injections or intravenous infusions, as appropriate.

Uniformity of mass

Powders for injections (single-dose use) comply with the test for uniformity of mass for single-dose preparations, unless otherwise specified in the individual monograph.

Uniformity of content

A requirement for compliance with the test for Uniformity of content for single-dose preparations is specified in certain individual monographs where the active ingredient is less than 40 mg. In such cases, compliance with the test for Uniformity of mass for single-dose preparations may not be required.

3.7.1 Lyophilization

Lyophilization or freeze drying is a process in which water is removed from a liquid product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. Lyophilization is a complex pharmaceutical process, its success requires control of the manufacturing process and filling processes for the liquid formulation and appropriate control during the lyophilization process. The process consists of three separate, unique, and interdependent processes; such as freezing, primary drying (sublimation), and secondary drying (desorption) (U. S. Department of Health and Human Sevices, 2009).

The advantages of lyophilization include:

- Enhanced stability of a dry powder;
- Removal of water without excessive heating of the product;
- Enhanced product stability in a dry state;
- Rapid and easy dissolution of reconstituted product.

Disadvantages of lyophilization include:

- Increased handling and processing time;
- Need for sterile diluent upon reconstitution;
- Cost and complexity of equipment.

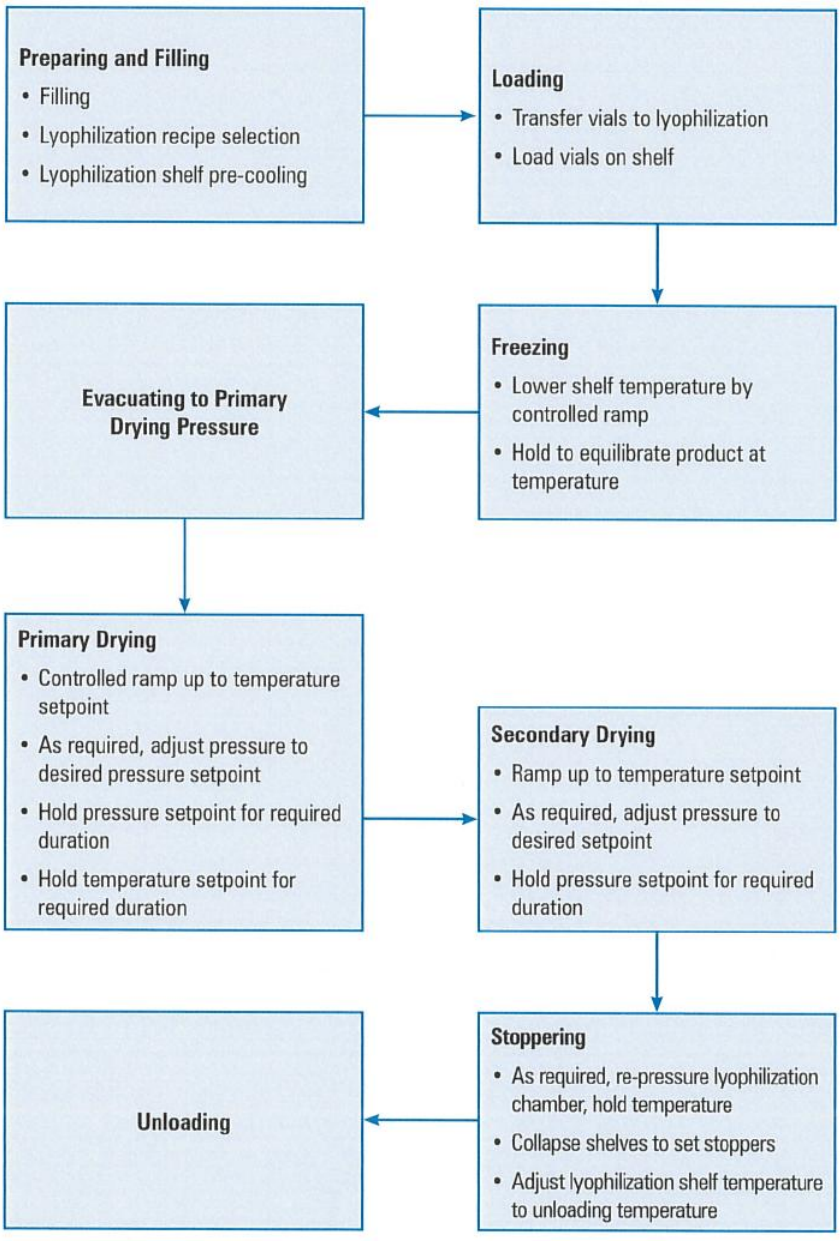


Figure 22: Process Flow Diagram: The Lyophilization Process

The lyophilization process generally includes the following steps (see also **Figure 22**):

- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through a 0.22 micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers.

It is recognized that there is complex technology associated with the manufacture and control of a lyophilized pharmaceutical dosage form. Some of the important aspects of these operations include: the formulation of solutions; filling of vials and validation of the filling operation; sterilization and engineering aspects of the lyophilizer; scale-up and validation of the lyophilization cycle; transfer and scale-up of the process to a larger-scale lyophilizer; and testing of the end product. This thesis will address some of the problems associated with the manufacture and control of a lyophilized dosage form.

Chapter 4 PARAMETERS AND METHODS – Quality Risk Management Tools

A successful validation program depends upon skilled interpretation of the information and knowledge gained from product and processes development regarding sources of variation, its impacts and associated risks. In agreement with that, this project aims to create a valuable risk tool to be used during lifecycle process validation to assess products' risk framework and also to provide an overview of the most critical process parameters of Hikma Injectables processes manufacturing.

Several risk Management Methods and Tools are available to support the various phases of the risk management process (*Section 4.5 - Risk Management Tools* Overview). In this thesis are also presented some of the most common statistical tools to be used in risk mitigation and process variability identification. A reliable process validation depends on the level of product and process knowledge the company has acquired from development studies and appropriate use of scientific data, risk management and statistical tools should be considered.

An improved system for Hikma Risk Analysis through product lifecycle that can be widely used and risks that are associated to Injectables Process Parameters are presented in *Chapter 5* – RESULTS – Assess Products` Risk Framework).

4.1 Critical Parameters

On one hand the specific modifications of CPP are connected to process variability, on the other hand CPP impact on CQA, enable its manipulation to ensure the state of control and product quality. Therefore, CPPs and CMAs for each unit operation or process step are evaluated in process validation studies. Screening experiments, product validation documentation, PQR, manufacturing productions of all types of Hikma products were used to determine CPPs. A risk-based approach for the identification of CPPs has been discussed for new products and existing products (see *Section 2.4.1 - STAGE 1: Process Design*). However, identification of CPPs is not a closed box and a continual search for new CPPs should be done over the product lifecycle and in parallel with product / process knowledge and experience.

Process parameters can be divided into three groups: parameters warranting multivariate evaluation, parameters whose ranges could be supported by univariate studies and parameters that do not require new studies, but instead would employ ranges based on knowledge space or modular claims established from prior knowledge. For an existing product, comparing the

normal operating range (NOR) to the proven acceptable range (PAR) should be considered when performing a risk assessment of potential CPPs (*Section 2.4.3.1 - Applying New Guidance to Old Products*). For a new manufacturing processes that are expected to consistently deliver the desired product quality, PAR should be wider compared to NOR (**Figure 24**). Some of the steps of drug product manufacturing are notoriously more difficult than others (Process Lifecycle Validation: Applying Risk Management, 2013).

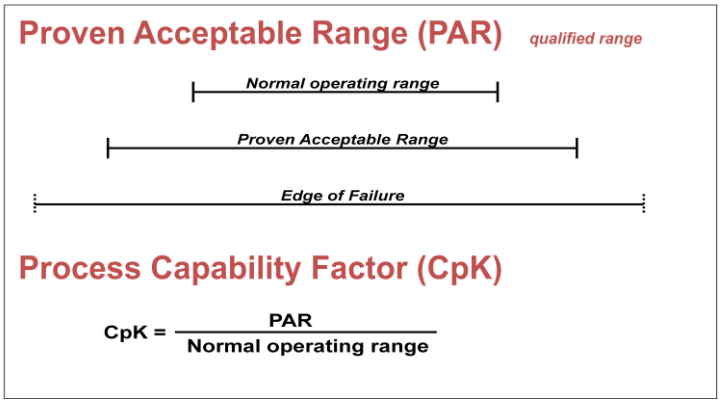


Figure 23: Process development Parameters – PAR (Proven Acceptable Range) and CpK (Process Capability Factor) – understanding of the process
(Deeks, 2006).

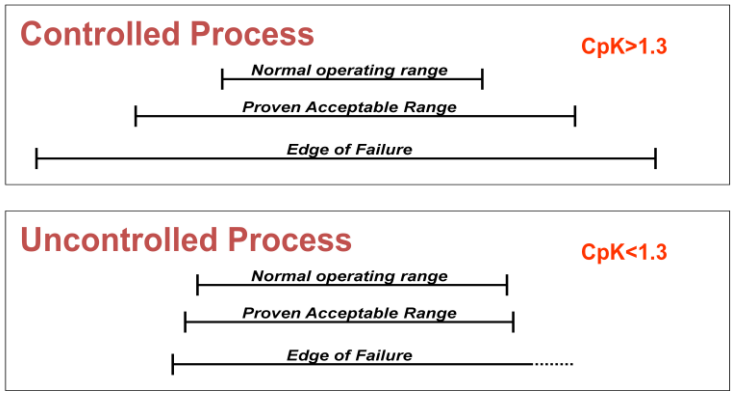


Figure 24: Process development Parameter – CpK (Process Capability Factor) – Controlled and Uncontrolled Process.
(Deeks, 2006).

4.2 Identifying Process Variation

Typical sources of injectable products variability may include process equipment capabilities and calibration limits, testing method variability, raw materials (e.g. API and excipient variability between lots and suppliers), human factors for non-automated processes, sampling variability, and environmental factors within plant facility. A Cause and Effect Diagram (**Figure 25**) can help the initial stages of variation identification and its relationship with process response.

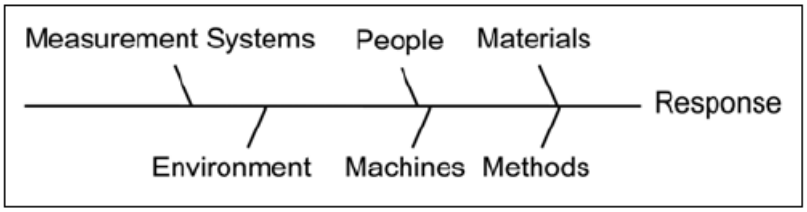


Figure 25: General Concept for Fishbone (Ishikawa) diagram (or Cause and Effect Diagram).

When a process is stable and in state of control, it displays common cause variation, variation that is inherent to the process. A process is in state of control when based on past experience it can be predicted how the process will vary (within limits) in the future. If the process is unstable, the process displays special cause variation, non-random variation from external factors. Here, control charts are simple, robust tools for understanding process variability.

4.2.1 The Four Process States

Processes fall into one of four states: 1) the ideal, 2) the threshold, 3) the brink of chaos and 4) the state of chaos (**Figure 26**).

When a process operates in the *ideal state*, that process is in statistical control and produces 100 percent conformance. This process has proven stability and target performance over time. This process is predictable and its output meets customer expectations.

A process that is in the *threshold state* is characterized by being in statistical control but still producing the occasional nonconformance. This type of process will produce a constant level of nonconformances and exhibits low capability. Although predictable, this process does not consistently meet customer needs.

The *brink of chaos state* reflects a process that is not in statistical control, but also is not producing defects. In other words, the process is unpredictable, but the outputs of the process still meet customer requirements. The lack of defects leads to a false sense of security; however, as such a process can produce nonconformances at any moment. It is only a matter of time.

The fourth process state is the *state of chaos*. Here, the process is not in statistical control and produces unpredictable levels of nonconformance.

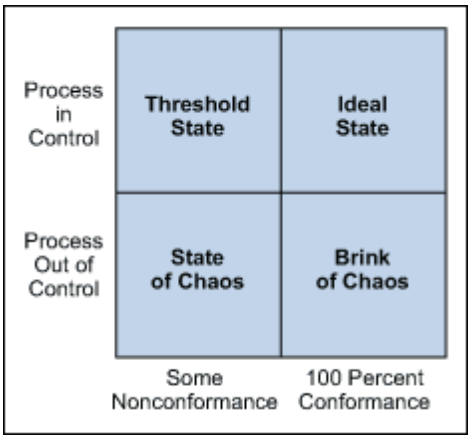


Figure 26: Four Process States

Every process falls into one of these states at any given time, but will not remain in that state. All processes will migrate toward the state of chaos (**Figure 27**). Companies typically begin some type of improvement effort when a process reaches the state of chaos (although arguably they would be better served to initiate improvement plans at the brink of chaos or threshold state). Control charts are robust and effective tools to use as part of the strategy used to detect this natural process degradation (Berardinelli, 2013).

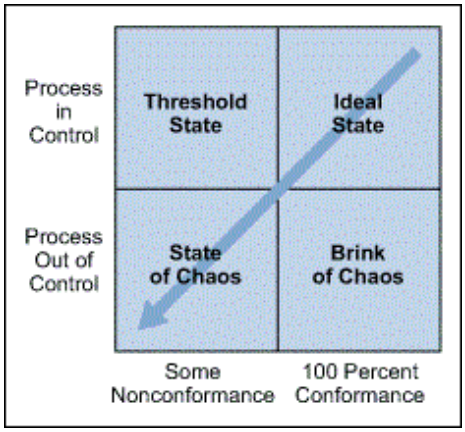


Figure 27: Natural Process Degradation

4.3 Control Charts

The most common risk assessment tools are check lists, which are a useful tool to help in hazards identification. There are other simple techniques used to structure risk management by organizing data and facilitating decision-making are flow-charts, check sheets, process-mapping and cause-effect diagrams.

Also, supporting risk tools are statistical tools as Control charts (c-charts, p-charts, np-charts, u-charts), Histograms and Pareto charts.

The most common application of control charts is to improve processes, as a tool to monitor process stability and state of control. A less common, although more powerful, use of control charts is as an analysis tool. The descriptions below provide an overview of the different types of control charts to support identification of the best chart for any monitoring situation, followed by a description of the method for using control charts for analysis (Berardinelli, 2013).

4.3.1 Elements of a Control Chart

There are three main elements of a control chart as shown in **Figure 28**.

1. A control chart begins with a time series graph.
2. A central line (X) is added as a visual reference for detecting shifts or trends – this is also referred to as the process location.
3. Upper and lower control limits (UCL and LCL) are computed from available data and placed equidistant from the central line. This is also referred to as process dispersion.

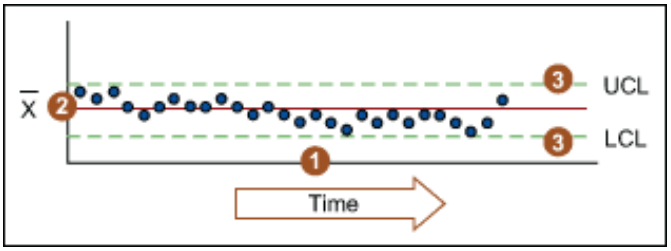


Figure 28: Elements of a Control Chart

Control limits (CLs) ensure time is not wasted looking for unnecessary trouble – the goal of any process improvement practitioner should be to only take action when warranted. Control limits are calculated by:

- Estimating the **standard deviation**, σ, of the sample data (at least 10 batches data);
- Multiplying that number by three;
- Adding (3 x σ to the average) for the UCL and subtracting (3 x σ from the average) for the LCL;

Mathematically, the calculation of control limits looks like:

$$\boldsymbol{CL = average \pm 3 \times \sigma}$$

Because control limits are calculated from process data, they are independent of customer expectations or specification limits.

Control rules take advantage of the normal curve in which 68.26 percent of all data is within plus or minus one standard deviation from the average, 95.44 percent of all data is within plus or minus two standard deviations from the average, and 99.73 percent of data will be within plus or minus three standard deviations from the average. As such, data should be normally distributed (or transformed) when using control charts, or the chart may signal an unexpectedly high rate of false alarms.

4.3.2 Controlled Variation

Controlled variation is described as a stable and consistent pattern of variation over time, and is associated with common causes. A process operating with controlled variation has an outcome that is predictable within the bounds of the control limits.

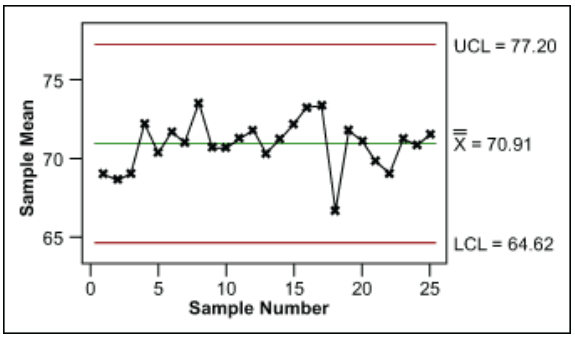


Figure 29: Example of Controlled Variation

4.3.3 Uncontrolled Variation

Uncontrolled variation is characterized by variation that changes over time and is associated with special causes. The outcomes of this process are unpredictable; a manufacturer may be satisfied or unsatisfied given this unpredictability.

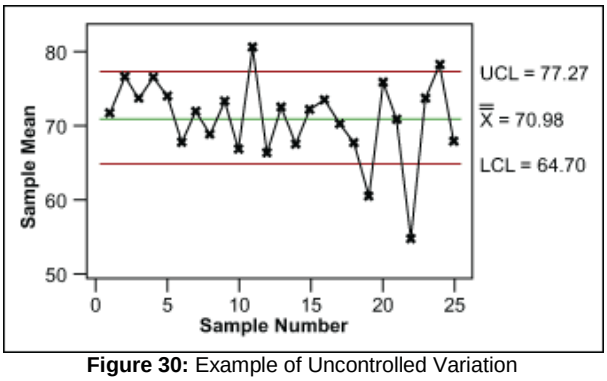


Figure 30: Example of Uncontrolled Variation

It is important to emphasize that process control and process capability are two different things. A process should be stable and in control before process capability is assessed.

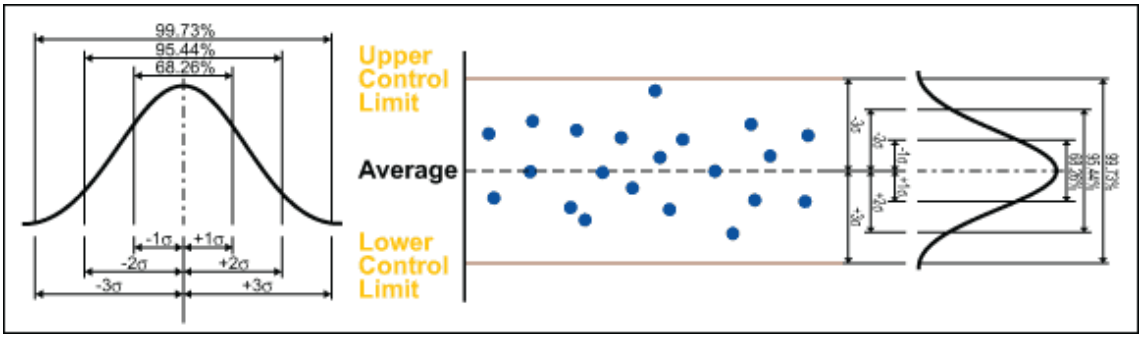


Figure 31: Relationship of Control Chart to Normal Curve

4.3.4 Control Charts for Continuous Data

4.3.4.1 Individuals and Moving Range Chart

The individuals and moving range (I-MR) chart is one of the most commonly used control charts for continuous data; it is applicable when one data point is collected at each point in time. The I-MR control chart is actually two charts used in tandem (**Figure 32**). Together they monitor the process average as well as process variation. With x-axes that are time based, the chart shows a history of the process.

The ***I chart*** is used to detect trends and shifts in the data, and thus in the process. The individuals chart must have the data time-ordered; that is, the data must be entered in the sequence in which it was generated.

The ***MR chart*** shows short-term variability in a process – an assessment of the stability of process variation. The moving range is the difference between consecutive observations. It is expected that the difference between consecutive points is predictable. Points outside the control limits indicate instability. If there are any out of control points, the special causes must be eliminated.

Once the effect of any out-of-control points is removed from the MR chart, the I chart should be evaluated and the process should be corrected.

The I-MR chart is best used when:

- The natural subgroup size is unknown.
- The integrity of the data prevents a clear picture of a logical subgroup.
- The data is scarce (therefore subgrouping is not yet practical).
- The natural subgroup needing to be assessed is not yet defined.

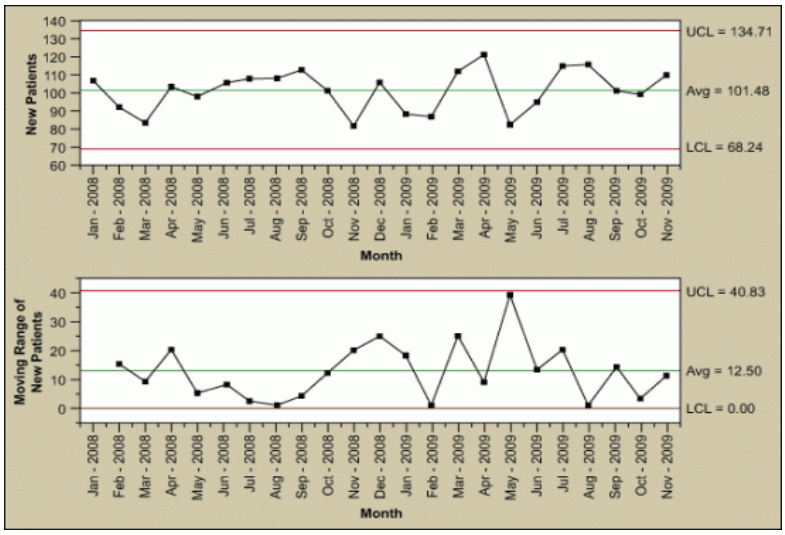


Figure 32: Example of Individuals and Moving Range (I-MR) Chart

Another commonly used control chart for continuous data is the Xbar and range (Xbar-R) chart (**Figure 33**). Like the I-MR chart, it is comprised of two charts used in tandem. The **Xbar-R chart** is used when you can rationally collect measurements in subgroups of between two and 10 observations. Each subgroup is a snapshot of the process at a given point in time. The chart's x-axes are time based, so that the chart shows a history of the process. For this reason, it is important that the data is in time-order.

The ***Xbar chart*** is used to evaluate consistency of process averages by plotting the average of each subgroup. It is efficient at detecting relatively large shifts (typically plus or minus 1.5 σ or larger) in the process average.

The ***R chart***, on the other hand, plot the ranges of each subgroup. The R chart is used to evaluate the consistency of process variation. Look at the R chart first; if the R chart is out of control, then the control limits on the Xbar chart are meaningless.

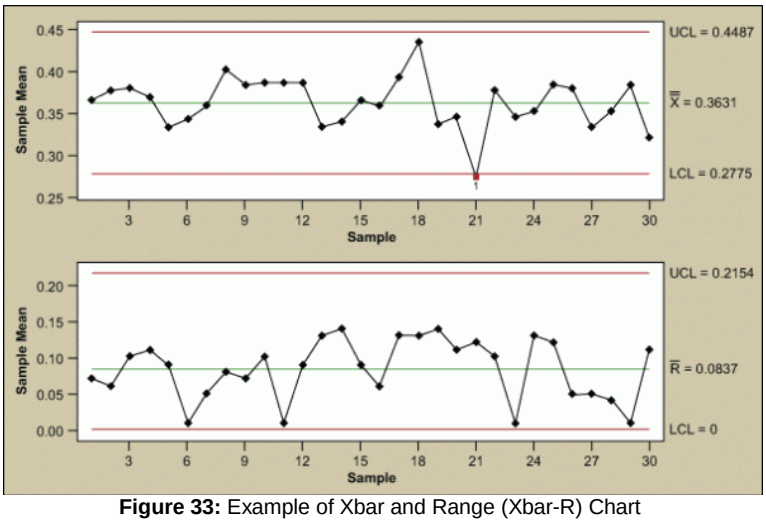


Figure 33: Example of Xbar and Range (Xbar-R) Chart

In

Table 2 shows the formulas to calculate the control limits. Many software packages do these calculations without much user effort. The control limits are a function of the average range (Rbar). This is the technical reason why the R chart needs to be in control before further analysis. If the range is unstable, the control limits will be inflated, which could cause an errant analysis and subsequent work in the wrong area of the process.

Table 2: Control Limit Calculations

	LCL	UCL
Xbar chart	$\bar{\bar{X}} - 3\frac{\bar{R}}{d_2}$	$\bar{\bar{X}} + 3\frac{\bar{R}}{d_2}$
R chart	$D_3\bar{R}$	$D_4\bar{R}$
I chart	$\bar{X} - 3\frac{\bar{R}}{d_2}$	$\bar{X} + 3\frac{\bar{R}}{d_2}$
MR chart	0	$D_4\bar{MR}$

Table 3: Constants for calculation Control Limits

Constants for Calculating Control Limits			
***n* (Sample Size)**	d_2	D_3	D_4
2	1.128	–	3.268
3	1.693	–	2.574
4	2.059	–	2.282
5	2.326	–	2.114
6	2.534	–	2.004
7	2.704	0.076	1.924
8	2.847	0.136	1.864
9	2.970	0.184	1.816
10	3.078	0.223	1.777
11	3.173	0.256	1.744
12	3.258	0.283	1.717
13	3.336	0.307	1.693
14	3.407	0.328	1.672
15	3.472	0.347	1.653

The I-MR and Xbar-R charts use the relationship of Rbar/d_2 as the estimate for standard deviation. The constant, d_2, is dependent on sample size. The difference between these two charts is simply the estimate of standard deviation.

4.3.5 Control Charts for Discrete Data

4.3.5.1 *c*-Chart

Used when identifying the total count of defects per unit (*c*) that occurred during the sampling period, the *c*-chart allows the practitioner to assign each sample more than one defect. This chart is used when the number of samples of each sampling period is essentially the same.

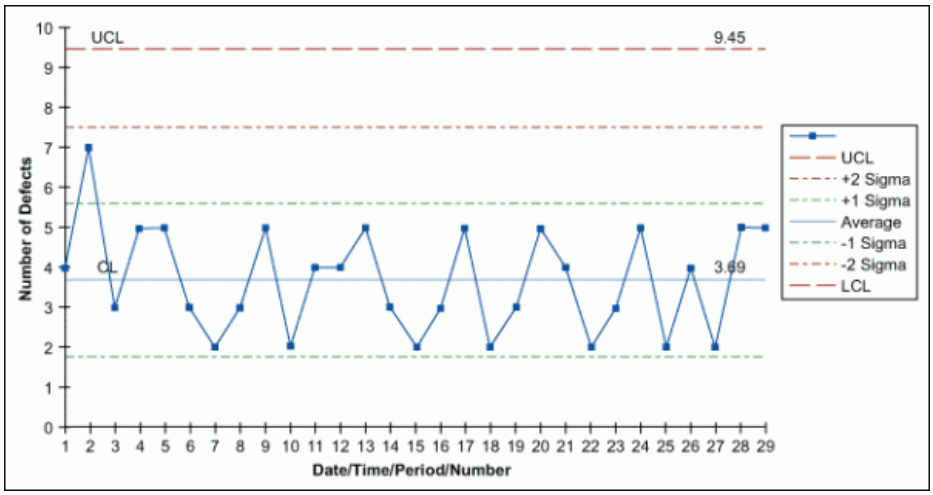


Figure 34: Example of *c*-Chart

4.3.5.2 *u*-Chart

Like *c*-chart, the *u*-chart is used to track the total count of defects per unit (*u*) that occur during the sampling period and can track a sample having more than one defect. However, unlike a *c*-chart, a *u*-chart is used when the number of samples of each sampling period may vary significantly.

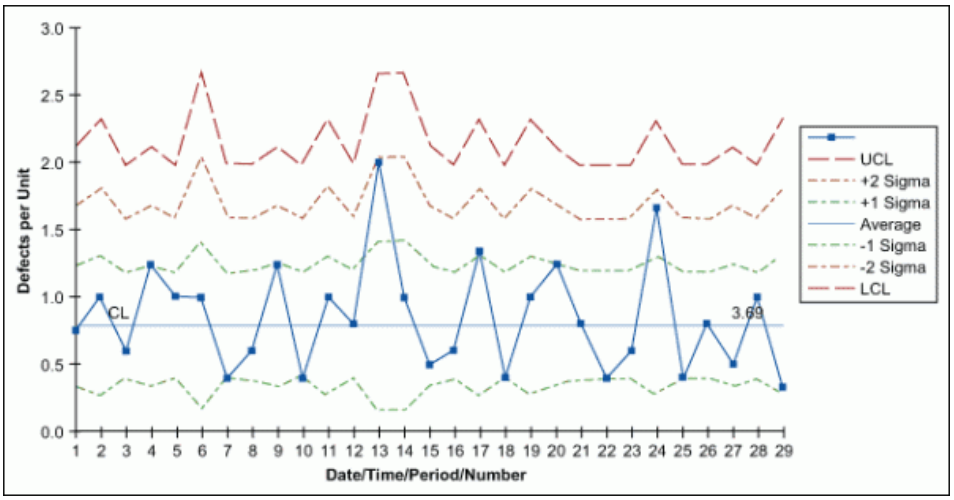


Figure 35: Example of *u*-Chart

4.3.5.3 np-*Chart*

Use an *np*-chart when identifying the total count of defective units (the unit may have one or more defects) with a constant sampling size.

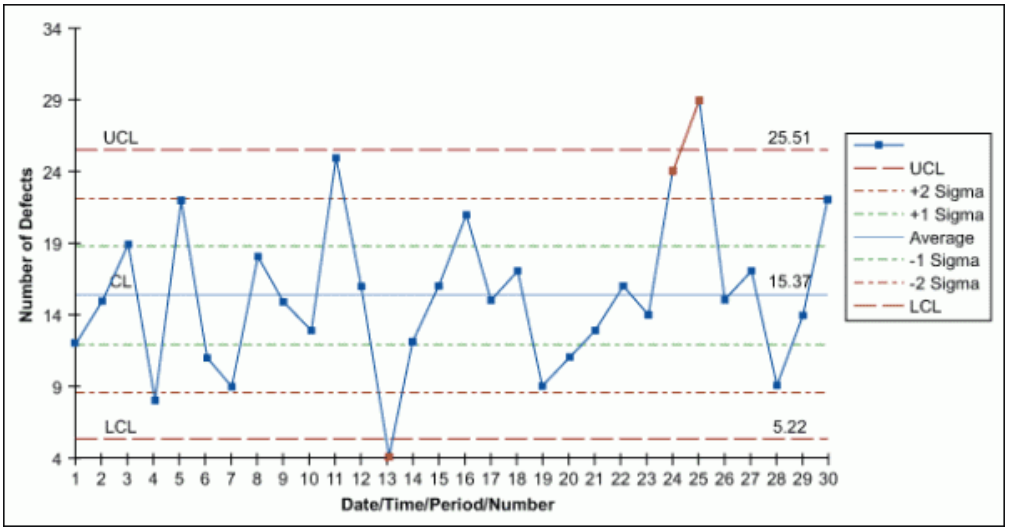


Figure 36: Example of *np*-Chart

4.3.5.4 *p*-Chart

Used when each unit can be considered pass or fail – no matter the number of defects – a *p*-chart shows the number of tracked failures (*np*) divided by the number of total units (*n*).

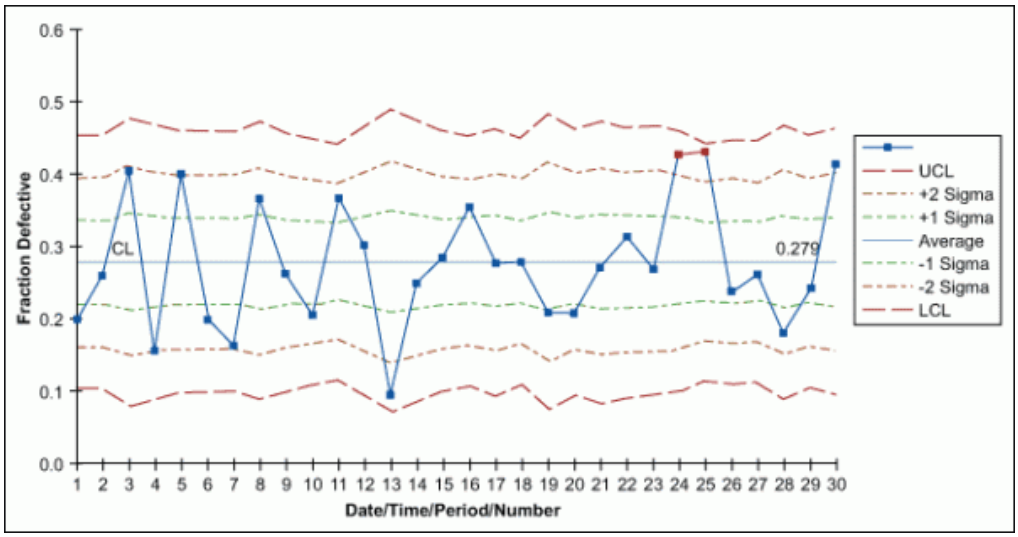


Figure 37: Example of *p*-Chart

4.3.6 Selection of a Control Chart

Although this chapter describes a plethora of control charts, there are simple questions a to be ask to find the appropriate chart for any given use. **Figure 38** walks through these questions and directs the user to the appropriate chart.

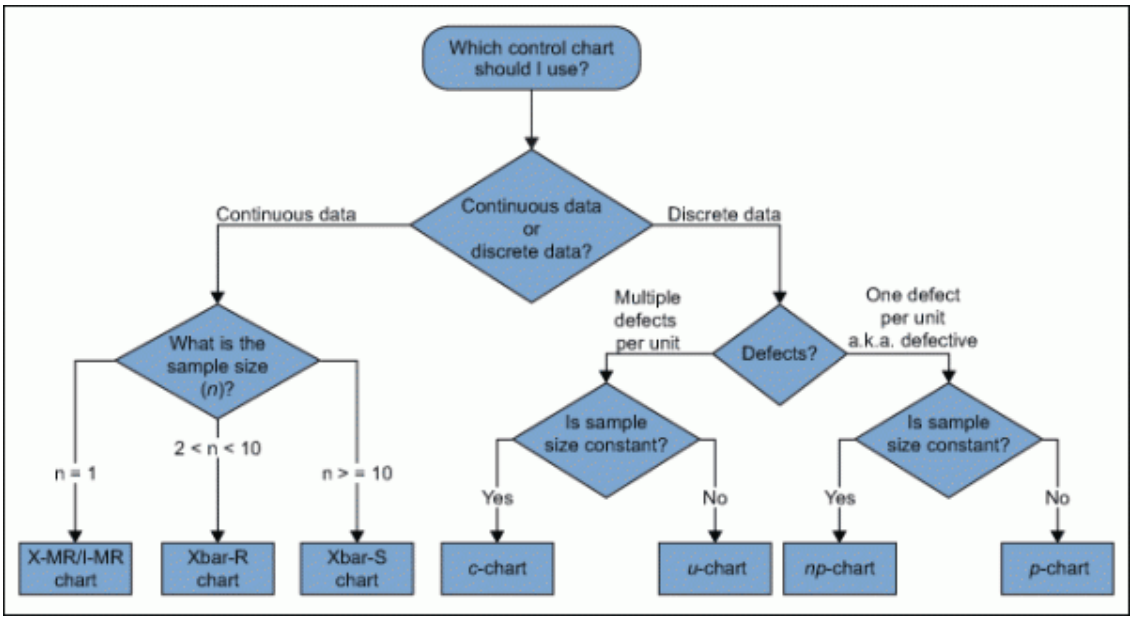


Figure 38: Mechanism for selection of the appropriate Control Chart

A number of points may be taken into consideration when identifying the type of control chart to use, such as:

- Variables control charts (those that measure variation on a continuous scale) are more sensitive to change than attribute control charts (those that measure variation on a discrete scale).
- Variables charts are useful for processes such as measuring tool wear.
- Use an individual chart when few measurements are available (e.g., when they are infrequent or are particularly costly). These charts should be used when the natural subgroup is not yet known.

A measure of defective units is found with *u*- and *c*-charts. In a *u*-chart, the defects within the unit must be independent of one another, such as with component failures. Use a *u*-chart for continuous items, such as fabric (e.g., defects per batches of years). A *c*-chart is a useful alternative to a u-chart when there are a lot of possible defects on a unit, but there is only a small chance of any one defect occurring (e.g., errors in a roll of material). These charting proportions, *p*- and *np*-charts are useful for e.g., compliance rates or process yields.

4.4 Control Charts as a Tool for Analysis

Subgrouping is the method for using control charts as an analysis tool. The concept of subgrouping is one of the most important components of the control chart method. The technique organizes data from the process to show the greatest similarity among the data in each subgroup and the greatest difference among the data in different subgroups.

The aim of subgrouping is to include only common causes of variation within subgroups and to have all special causes of variation occur among subgroups. When the within-group and between-group variation is understood, the number of potential variables – that is, the number of potential sources of unacceptable variation – is reduced considerably, and where to expend improvement efforts can more easily be determined.

4.4.1 Within-subgroup Variation

For each subgroup, the within variation is represented by the range. The R chart displays change in the within subgroup dispersion of the process and answers the question: Is the variation within subgroups consistent? If the range chart is out of control, the system is not stable. It tells you that you need to look for the source of the instability, such as poor measurement repeatability. Analytically it is important because the control limits in the X chart are a function of R-bar. If the range chart is out of control then R-bar is inflated as are the control limit. This could increase the likelihood of calling between subgroup variation within subgroup variation and send you off working on the wrong area.

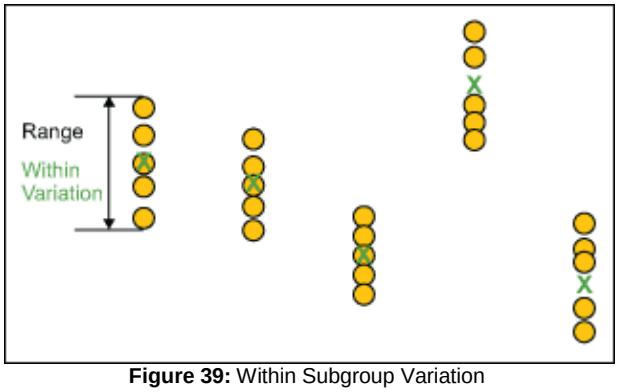


Figure 39: Within Subgroup Variation

Within variation is consistent when the R chart – and thus the process it represents – is in control. The R chart must be in control to draw the Xbar chart.

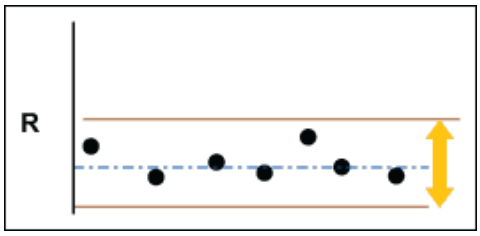


Figure 40: Example of R Chart

4.4.2 Between Subgroup Variation

Between-subgroup variation is represented by the difference in subgroup averages.

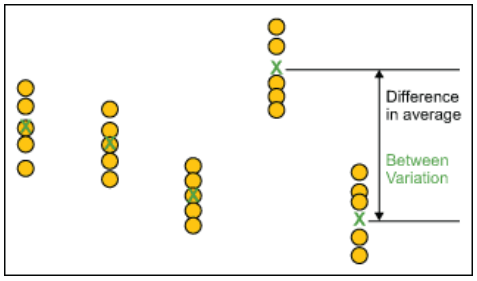


Figure 41: Between Subgroup Variation

4.4.3 Xbar Chart – other use

The Xbar chart shows any changes in the average value of the process and answers the question: Is the variation between the averages of the subgroups more than the variation within the subgroup? If the Xbar chart is in control, the variation "between" is lower than the variation "within." If the Xbar chart is not in control, the variation "between" is greater than the variation "within."

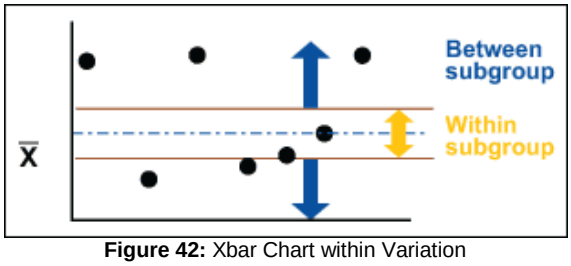


Figure 42: Xbar Chart within Variation

In conclusion knowing which control chart to use in a given situation will assure accurate monitoring of process stability. It will eliminate erroneous results and wasted effort, focusing attention on the true opportunities for meaningful improvement.

4.5 Risk Management Tools Overview

Risk tools are traditionally categorized as simple or detailed. Simple tools are often used as a precursor to using the detailed tools or early in development where little is known about processes, materials, and products. The list below (**Figure 43**) is not exhaustive and the output *Simple Risk Tools* are not particularly quantitative and are normally for identification or hazards and/ or risks only. These tools are extremely simple to use and yield results quickly.

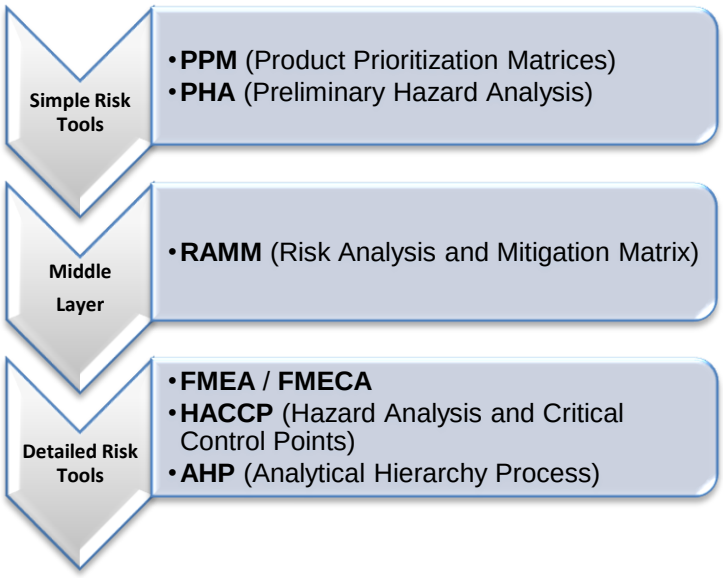


Figure 43: Risks hierarchy
(Brindle, et al., 2012)

More detailed tools are used for comprehensive risk analysis, mitigation steps and include a quantitative calculation. Examples of these tools include FMEA (Failure Modes and Effects Analysis), FMECA (Failure Modes, Effects and Criticality Analysis), HACCP (Hazard Analysis and Critical Control Points) and AHP (Analytical Hierarchy Process). The use of these tools enables a comprehensive analysis of risk. All of these risk tools, either simple or detailed, can be complemented by a middle level risk tool RAMM (Risk Analysis and Mitigation Matrix) (Brindle, et al., 2012). RAMM aligns with ICH and FDA guidances (Q8 to Q10 and Process Validation); especially tracking Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) in a pragmatic approach.

4.5.1 Product Prioritization Matrices (PPM)

A Prioritization Matrice can help decisions about what to do after key actions, criteria or Critical-To-Quality (CTQ) characteristics have been identified, but their relative importance (priority) is not known with certainty. This tool is used to prioritize items and describe them in terms of weighted criteria. It uses a combination of tree and matrix diagramming techniques to

do a pair-wise evaluation of items and to narrow down options to the most desired or most effective.

To create a matrix, a judgment of the relative ability of each possible action comparing to every other identified action is performed to effectively deliver the results wanted. The parameter is a weighted ranking of all the possible actions considered. The finished matrix can help a team make an overall decision or determine the sequence in which to attack a problem or work toward an objective.

Therefore this tool should be used when:

1. The key root causes have been identified and the most critical causes have been narrowed down.
2. When the issues are complex and they have strong interrelationships.
3. There are very limited resources for improvement activities and hence the team must concentrate on the critical few.

4.5.2 Preliminary hazard Analysis (PHA)

This tool analysis is based on applying prior experience or knowledge of hazard to identify future hazards, hazardous situation. Also, it can be used for product, process and facility design. Another application is in early development of the project where there is little information on detail available. PHA is a semi-quantitative analysis that is performed to: identify all potential hazards and accidental events that may lead to an accident; rank the identified accidental events according to their severity, and identify required hazard controls and follow-up actions (**Table 4**) (Kirupakar, 2007).

Table 4: Typical PHA worksheet

System:			***Operating mode:***			***Analyst/ Date:***	
Product	***Hazard***	***Accidental event (what, where, when)***	***Probable causes***	***Contingencies / Preventive actions***	***Probability***	***Severity***	***Comments***
…	**…**	**…**	**…**	**…**	**…**	**…**	**…**

4.5.3 Risk Analysis and Mitigation Matrix (RAMM)

The Risk Analysis and Mitigation Matrix (RAMM) was developed to be quantitative yet simple to use. The RAMM tool is potentially a useful compliment to the other risk tools and can

be used solely or in combination with other risk tools. The potential to use something quantitative, but not as complex as the detailed risk tools can potentially serve as the useful keystone of a risk management system as it is quantitatively yet manageable(Brindle, et al., 2012).

The tool can be applied in six stages as part of a risk management system:

Stage 1 – Team and Knowledge – – Selecting the right team to be involved with RAMM workshop sessions. It is important that these individuals get an opportunity to "walk the process" so they get an understanding of what they are dealing with in terms of how the process is run on a daily basis.

Stage 2 – Identifying the CQAs – Desired CQAs.

Stage 3 – Define the Process Steps – Evaluation of process development and manufacturing to prepare the actual process, which would be the central point of the RAMM

Stage 4 – Define Process and Material – Once the overall process is defined, each process should be broken down into process parameters (some of which would become critical process parameters) and other important parameters.

Stage 5 – Create RAMM and Score it – The RAMM uses a matrix of process input factors and quality attributes to assess risk and impact.

Table 5: CQAs and relative criticality

Relative importance of CQA	**9**	**1**	**3**	**9**	**9**
Process Parameters or Material Attribute	**Purity Assay**	**Visual Appearenc**	**pH**	**Sterility**	**Endotoxins**

At this stage the RAMM could be sorted and filtered so that process inputs can be assessed by their impact on a specific response, by the interim process step, or for their overall impact on the entire process. Likewise, the matrix could be filtered to determine which process step or input factors had the greatest impact on a particular attribute.

Table 6: Short e.g. of process parameters with CQAs with risk scores detailed for just one process step (compounding).

		Relative importance of CQA	**9**	**1**	**9**	**3**	**9**	**9**	**9**	
Process step	**Class**	**Process Parameters or Material Attribute**	**Assay (HPLC)**	**Visual appearence**	**Purity**	**pH**	**Bioburden**	**Free from Particles**	**Endotoxins**	**TOTAL**
Compounding	Personal	Equipment cleaning	1	1	1	1	9	1	9	23
Compounding	Procedure	Bulk solution final volume	9	1	1	3	1	1	1	17
Compounding	Procedure	pH adjustment	3	1	1	9	1	1	1	17
Compounding	Procedure	Raw-materials dissolution	9	3	1	6	1	3	1	24

Stage 6 – Mitigation – The key action designed should be around gaining improved process robustness. In order to improve this, experiments were defined. Additionally, it was indicated that some changes to the equipment would improve the equipment setup weaknesses.

The RAMM can be integral part of an effective quality management system, facilitating implementation of the enabling concepts, knowledge management and quality risk management.

4.5.4 Failure Mode Effects Analysis (FMEA)

FMEA depends on product and process understanding. It methodically breaks down the analysis of complex processes into manageable steps. It provides evaluation of potential failure modes for processes and their likely effect on product performance. FMEA considers each mode of failure of every component of a system and ascertains the effects on the systems operation of each failure mode in turn therefore it is a systematic method of identifying and preventing products and process problems before they occur. This tool is further advanced with studying criticality of the consequences and providing clear indication of the situation.

The application consists in:

- Decision team;
- Identification of potential Failure Modes, Consequences and Causes;
- Classification of each failure mode – Severity, Occurrence and Detection;
- Calculation of Parameter of Priority Risk (RPN);
    - Classification of each criterion
    - Multiplication of weights
    - **RPN = Severity x Occurrence x Detection** It will be obtained a number between 1 and 125. The higher the number, more serious the failure mode will be.

In this way it is possible to establish priorities of action and implement a control risk status associated to the critical activity.

Some benefits of performing FMEA analysis include higher reliability, better quality, increased safety and its contribution towards cost saving includes decreased development time and non value added operations.

4.5.5 Failure Mode Effects and Criticality Analysis (FMECA)

It is the extension of the above FMEA tool. Extending FMEA to incorporate an investigation of the degree of severity of consequences, their probabilities of occurrence and their detectability is Failure mode, effects and criticality analysis. In FMECA, each failure mode of the product is identified and then evaluated for criticality. This criticality is then translated into a risk, and then translated into a risk, and if this level of risk is not acceptable, corrective action must be taken. This can be utilized for failure and risk associated with manufacturing processes. The tool can also be used to establish and optimize maintenance plans for repairable systems and/or contribute to control plans and other quality assurance procedures. In addition, an FMEA or FMECA is often required to comply with safety and quality requirements, such as ISO 9001, Six Sigma, FDA Good Manufacturing Practices (GMPs).

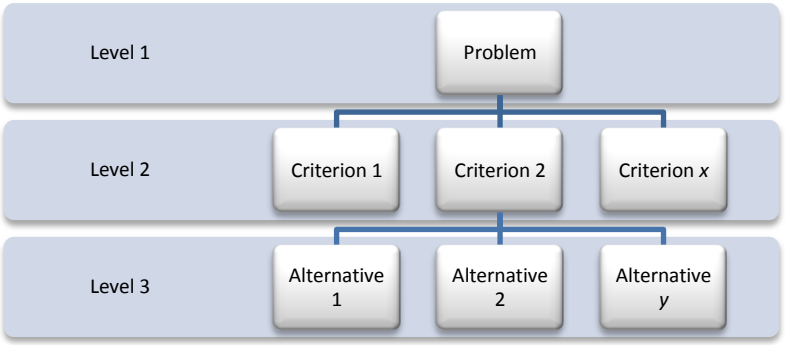
4.5.6 Analytical Hierarchy Process (AHP)

Analytical Hierarchy Process (AHP) is a model to quantify situations involving multiple criteria for organizing and analyzing complex processes. Rather than prescribing a “correct” decision, the AHP helps finding the decision that suits the goal and their understanding of the problem. It provides a comprehensive and rational framework for structuring a decision problem, for representing and quantifying its elements, for relating those elements to overall goals, and for evaluating alternative solutions.

There are 4 steps to be followed while implementing the AHP process:

1- Decision Hierarchy

- Break down the problem into decision elements – criteria and alternatives
- The overall goal is placed at the top; the remaining attributes bellow
- $x + 1 = Criteria\ matrix + Alternative\ matrixes$



2- Pairwise Comparisons of Decision elements

- Compare all pairs of elements in one level with respect to the previous level
- The comparisons are organized in matrixes $n \times n$ (n = number of alternatives in each level)
- Main diagonal must consist 1.

	1	2	…	n
1	1	A_{12}	…	A_{1n}
2	a_{21}	1	…	A_{2n}
…	…	…	1	…
n	a_{n1}	a_{n2}	…	1

- Comparison based in a 1 to 9 scale – Saaty`s scale:

Intensity of relative importance	Definition
1	Equally important
2	Intermediate importance value
3	A is weekly more important than B
4	Intermediate importance value
5	A is moderately more important than B
6	Intermediate importance value
7	A is strongly more important than B
8	Intermediate importance value
9	A is absolutely more important than B

3- Assessment of the Consistency of Decisions taken

Decisions taken by the decision elements Valid and Consistent

- Consistency Ratio (CR) correspondent to each matrix:

$$CR = \frac{CI}{RI} = \frac{{}^{(\lambda_{máx}-n)}/_{(n-1)}}{RI} \leq 0.10 \qquad \text{with } \lambda_{máx} \geq n$$

In which:

$\lambda_{máx}$- largest or principal eigenvalue

CI- Constancy index

RI- Random consistency index

n –order matrix

- Typical values for the RI

N	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
RI	0	0	0.58	0.90	1.12	1.24	1.32	1.41	1.45	1.49	1.51	1.48	1.56	1.57	1.59

4- Determination of relative weights

$$Priotitie\ Vector = \frac{\sum all\ entreis\ of\ a\ row}{\sum all\ entries\ of\ the\ matrix}$$

	A	B	C	D	PV
A	**1**	**5**	**7**	**9**	**0.589**
B	**1/5**	**1**	**3**	**5**	**0.247**
C	**1/7**	**1/3**	**1**	**3**	**0.120**
D	**1/9**	**1/5**	**1/3**	**1**	**0.044**
					1

4.5.7 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive and preventive tool for assuring quality, reliability and safety. It involves hazard analysis, determining critical control point, establishing critical limit, establishing a system to monitor critical control point and establishing a record keeping system. This might be used to identify and manage risk associated with physical, chemical and biological hazards.

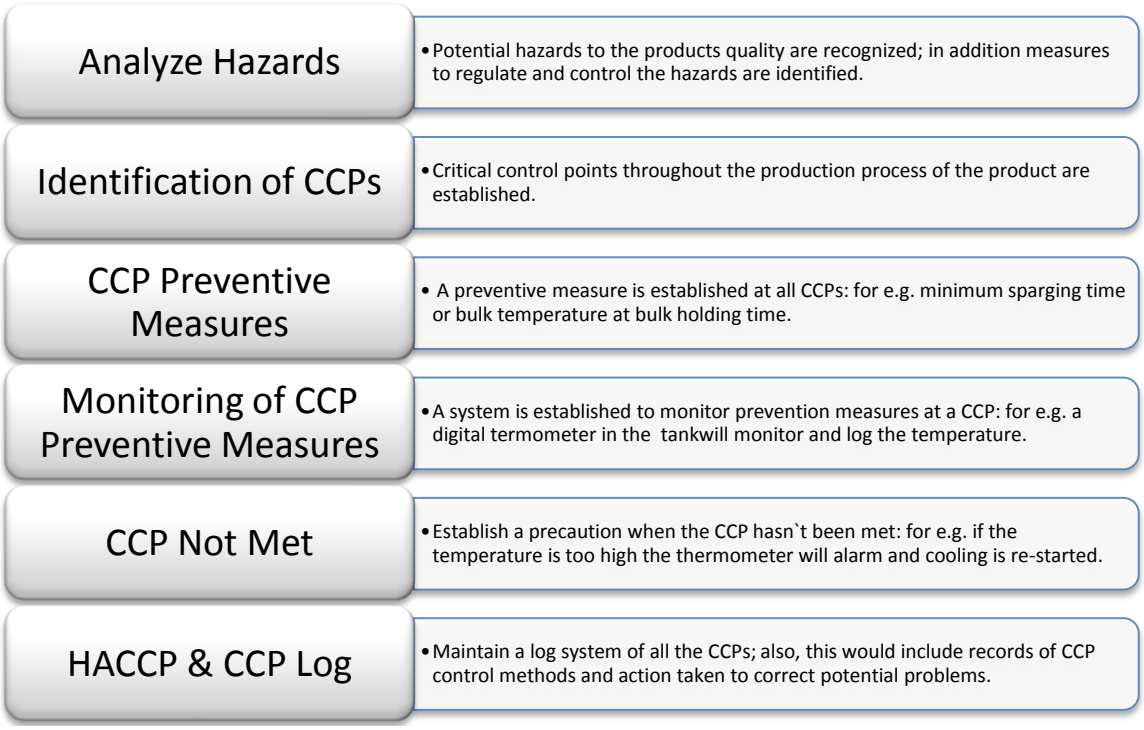


Figure 44: HACCP Seven Principles

Chapter 5 RESULTS – Assess Products` Risk Framework

The goal of Hikma Risk Analysis approach is aligned with ICH and FDA guidelines described in *Chapter 2 - LITERATURE OVERVIEW*; especially around tracking Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) in a pragmatic manner.

5.1 Injectables Manufacturing Processes

In order to evaluate the risks associated to the sterile production of injectable products, it is crucial to identify the operational pharmaceutical units of the process. There are raw-materials and inputs, process controls, and product attributes associated with every unit operation in a manufacturing process. In **Figure 45** it is exemplified a process flow-chart for an injectable product.

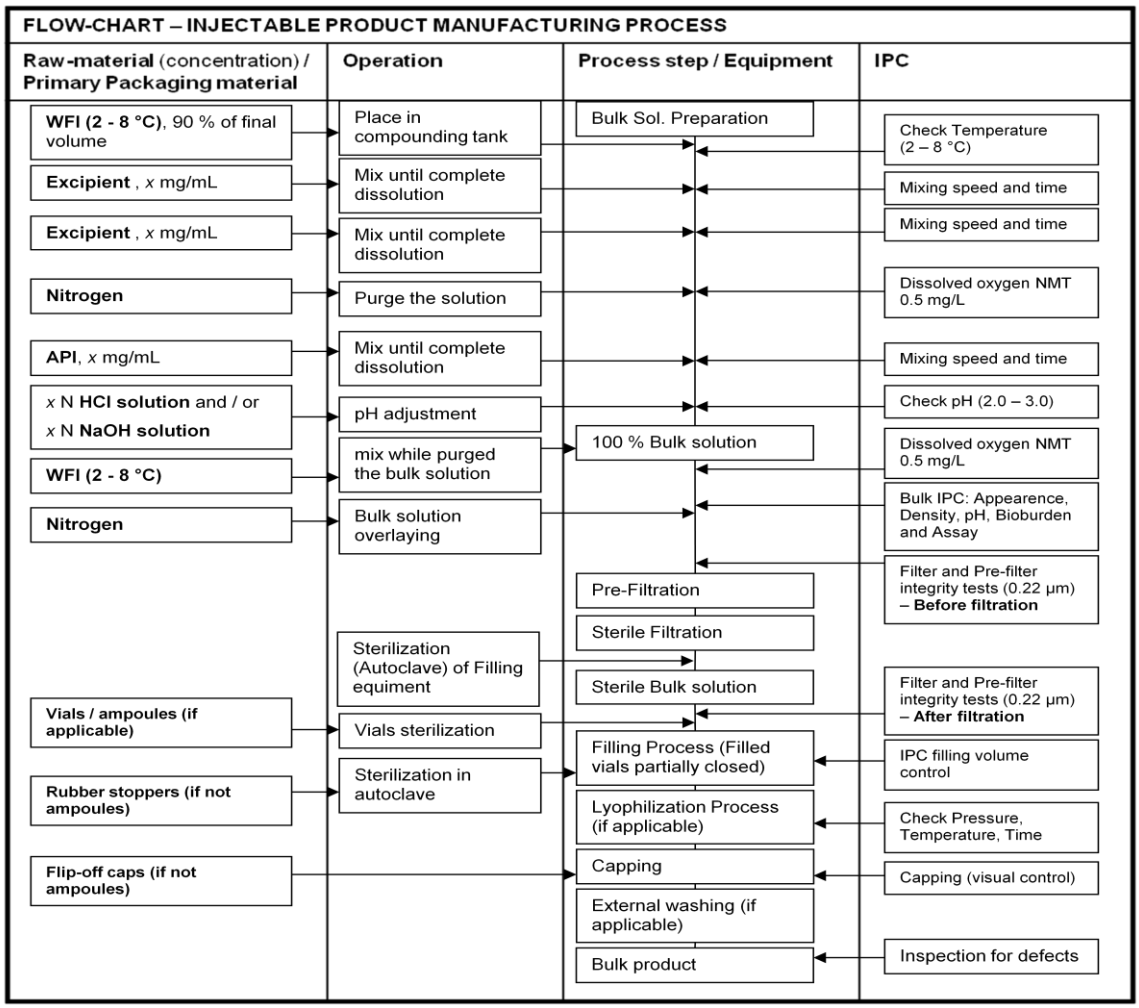


Figure 45: Flow-chart e.g. of an Injectable Manufacturing Process

A typical process consists of a series of unit operations. In order to develop a robust process, units of operations have to be studied and the process parameters and attributes have to be defined. In general, flow charts are used to define the process. This flow-chart should have sufficient detail to readily understand the primary function of each step. **Figure 45** illustrates a general process flow-chart for HIKMA injectable product. It is important to underline that all components and processes involved in the preparation of injectable products must be selected and designed to eliminate, as much as possible, contamination of all types. Aseptic processing is the most demanding of pharmaceutical processes. It requires precise attention to operator training and behaviour, process validation, production process documentation, plant and equipment maintenance and quality risk managing the changes.

5.2 Injectable Manufacturing Variables: Sources

To meet the requirement of exhaustiveness of hazards and risks evaluation and reviewing, the project methodology initially proceeded to the inventory of all activities implemented in the process covered by Hikma quality system.

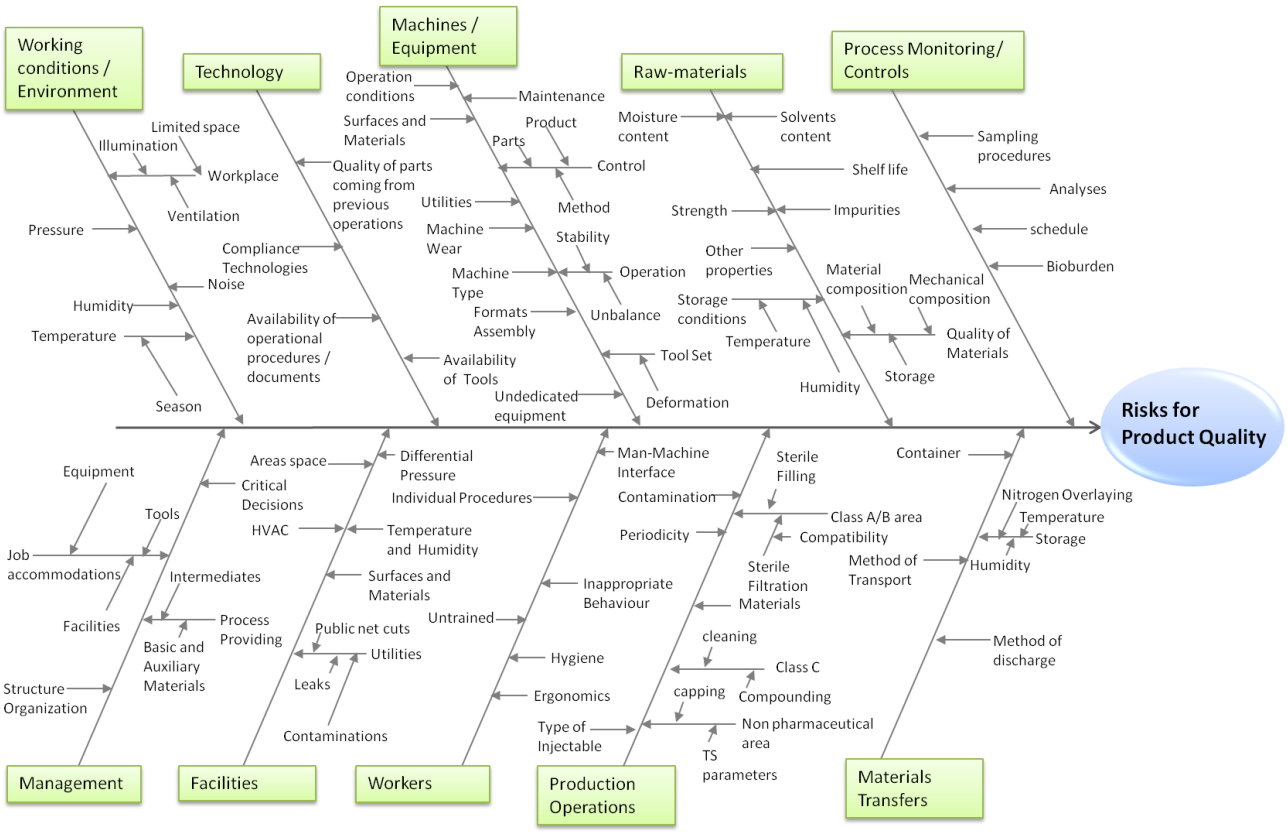


Figure 46: Cause and Effect Diagram with CPP from Manufacturing Process of Injectable Products

The process operations are considered the major contributors that cause the starting materials to be converted to final product. Although this seems complex at first, manufacturing processes of different injectable forms share some similar process steps. The scope to assess products risks` framework starts by understanding and evaluating process inputs in order to set the control strategy. It is this combination of process inputs and CQA, complemented by a control strategy that proves a manufacturing quality new product or at commercial scale. In **Figure 46** are identified the general causes of Hikma injectable products and processes that may have an impact on product quality.

5.3 Critical Process Parameters (CPPs)

A list of general Process Parameters common to Hikma Injectables manufacturing was listed (**Figure 7**), which are potential CPPs dependent on the product specificities. The in-process and finish product controls monitor the process but the aim of this project is to reduce the risk to an acceptable level by introducing additional controls in the manufacturing process, facility or equipment. According to a risk evaluation this potential CPPs may turn out to be considered CPPs or CCPs (Critical Control Parameters). These activities were divided into elementary steps, which are then individually introduced in the decisional risk assessment tool.

Table 7: Specifications of Process Parameters and general IPC and Finish Product Controls

Manufacturing Process Activities	Common Process Parameters for Injectable Products (potential CPPs)	Controls of Intermediate Products and Finished Products
Materials / Equipment preparation	• Temperature / time of material sterilization • Define Sterilization loads • Clean and dirty hold time • Equipment drying time • Cleaning processes • Weighing of Raw-materials • Materials compatibility	Bioburden Endotoxins Cross-contamination
Compounding	• Stainless steel tank • Mixing speed / time • Flow of Nitrogen • Total holding time • Light sensitivity • Heat / cold sensitivities • Samples storage conditions	Temperature Dissolved Oxygen Assay Density pH Assay Related substances
Filtration	• Filtered compressed Air / Nitrogen • Filters (autoclaved) drying time • Filters contact time	Assay Density pH

Manufacturing Process Activities	Common Process Parameters for Injectable Products (potential CPPs)	Controls of Intermediate Products and Finished Products
	• Filter Compatibility with product • Filtration pressure • Filtration flow-rate • Filtration temperature (according to validation) • Type of sterilizer filter • Integrity test to the filter • Aseptic technique	Bioburden Filter validation studies
Filling	• Temperature • Fill volume • Speed of filling • Nitrogen overlaying • Aseptic technique	Volume / Weight variation Color/ clarity (if applicable) Assay Related substances / Purity pH Oxygen headspace Endotoxins Sterility
Lyophilisation (if applicable)	• Product temperature • Freeze dryer shelves temperature • Chamber pressure	Appearance Reconstitution time Leak test Uniformity of content Uniformity of mass Assay Water content pH Related substances Particles after reconstitution Endotoxins Sterility
Final Sterilization (if applicable)	• Temperature / time of product sterilization	Sterility Assay Related substances
Inspection	• Finish Product quality attributes – optical inspection machine / visual inspections	Particles Defects

In agreement to Process Validation guidance from FDA (Guidance for Industry - Process Validation: General Principles and Practices, January 2011) quality cannot be adequately assured merely by in-process and finished-product inspection or testing as described summarily in the above table (**Table 7**). Quality cannot be tested into products; it should be built-in or design-in.

A risk analysis prepared in this work will comprehensively identify and document risks, and furthermore, develop solutions that can reduce or eliminate the identified risks and minimise the scope of the subsequent qualification testing. Arriving at an accurate risk profile is difficult, but needed, to identify risk and subsequently manage or mitigate the threats and vulnerabilities that create potential variability. The difficulties of creating a risk profile for each injectable product will be minimized or even outdated with *Hikma Risk Assessment Tool* created in this project.

5.4 Hikma Risk Approach – Assess Products` Risk Framework over entire Product Lifecycle

Process validation demonstrates consistency of the process at NOR. Lifecycle approach makes process validation an ongoing activity that enables ongoing assurance gained since the first produced batches (Product Performance Qualification) during routine production that the process remains on state of control (**Figure 47**).

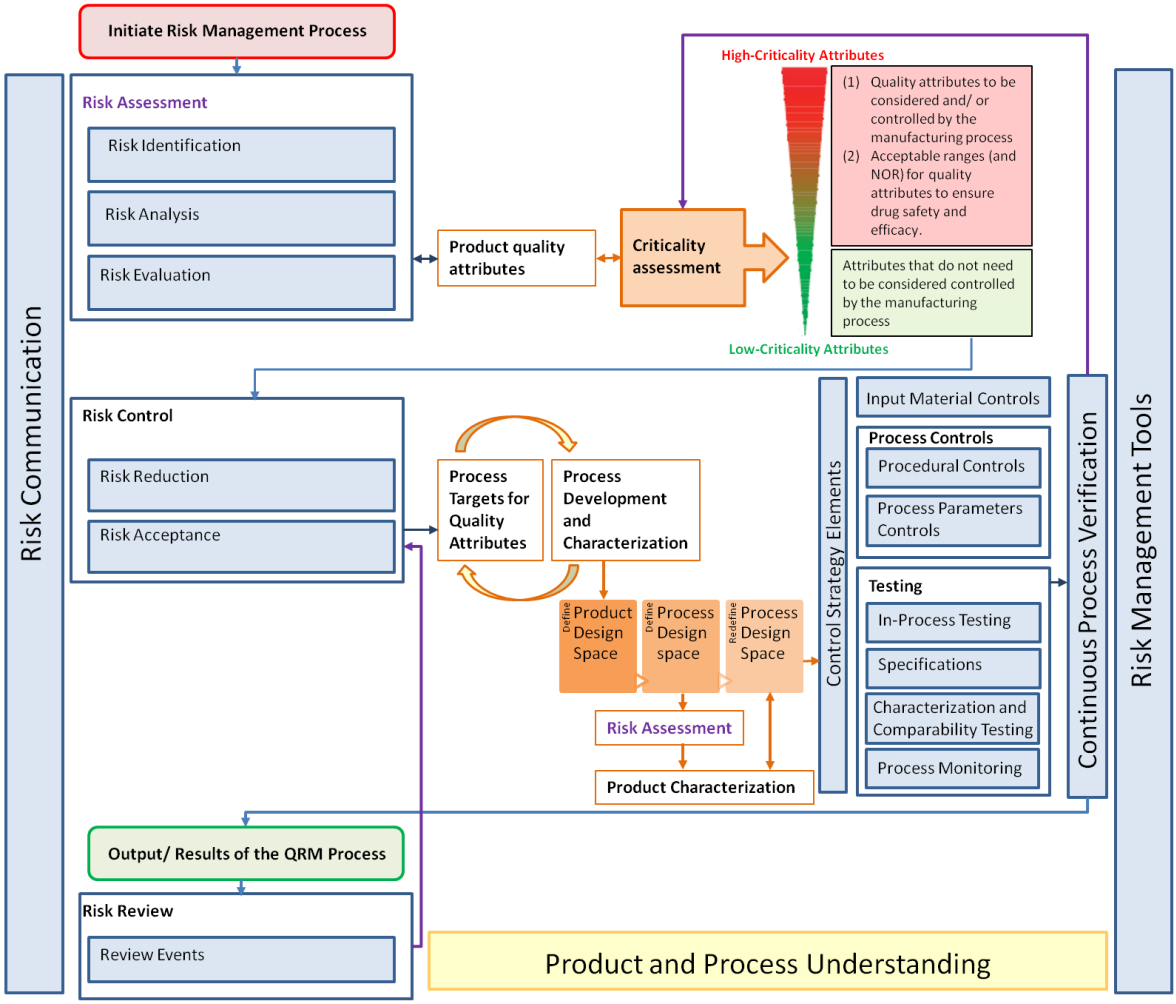


Figure 47: Strategy approach for products design space verification over lifecycle of different forms of Hikma Injectable Products - Hikma Process Validation Program of Injectable Products Lifecycle.; no temporal relationship is intended.

Each process designed intents to define the commercial process on knowledge gained through development and scale-up activities. The outcome is the design of a reproducible process suitable for routine manufacture that will consistently deliver product that meets its CQA. Once a manufacturing process has been tested to the extent that the test results are predictable, further testing can be replaced by establishing that the system was operating within a defined design space. Based on this scheme on **Figure 47** was designed to clarify the suggested procedure to build quality into processes - Hikma Process Validation Program of Injectable Products Lifecycle.

In both (FDA and EMA) agencies` experience, the design space verification at commercial scale is not necessarily complete at the time of submission of the product but should happen over its lifecycle. However, movements from one NOR to another NOR within the approved design space (in an unverified area) may pose higher or/ and unknown risks due to potential scale-up effects, new equipments, model assumptions, etc. Also, three batches run early in lifetime of a product cannot be expected to represent its process a decade later or beyond. Therefore FDA and EMA came with the announcement, last October (2013) for a new guideline in which is described that is essential to understand and evaluate those risks, utilizing an appropriate control strategy, including but not restricted to the controls submitted in the dossier.

Moreover, Hikma must be able to adequately explain and defend the choices that it makes to the authorities. In the end it is the data and the operational metrics that are taking in consideration and not the number of batches. This is achieve by this systematic approach to development that begins with predefined QTPP and emphasize the product and process understanding and its controls based on quality risk management and science. In addition, look to process parameters and unit operations that impact CQA and further control strategies will support the choice of operating range that is critical and must be verified over product lifecycle for commercial scale. In practice, the suggested approach for QRM in Hikma to evaluate and improve the quality assurance of production can progress following some initial steps:

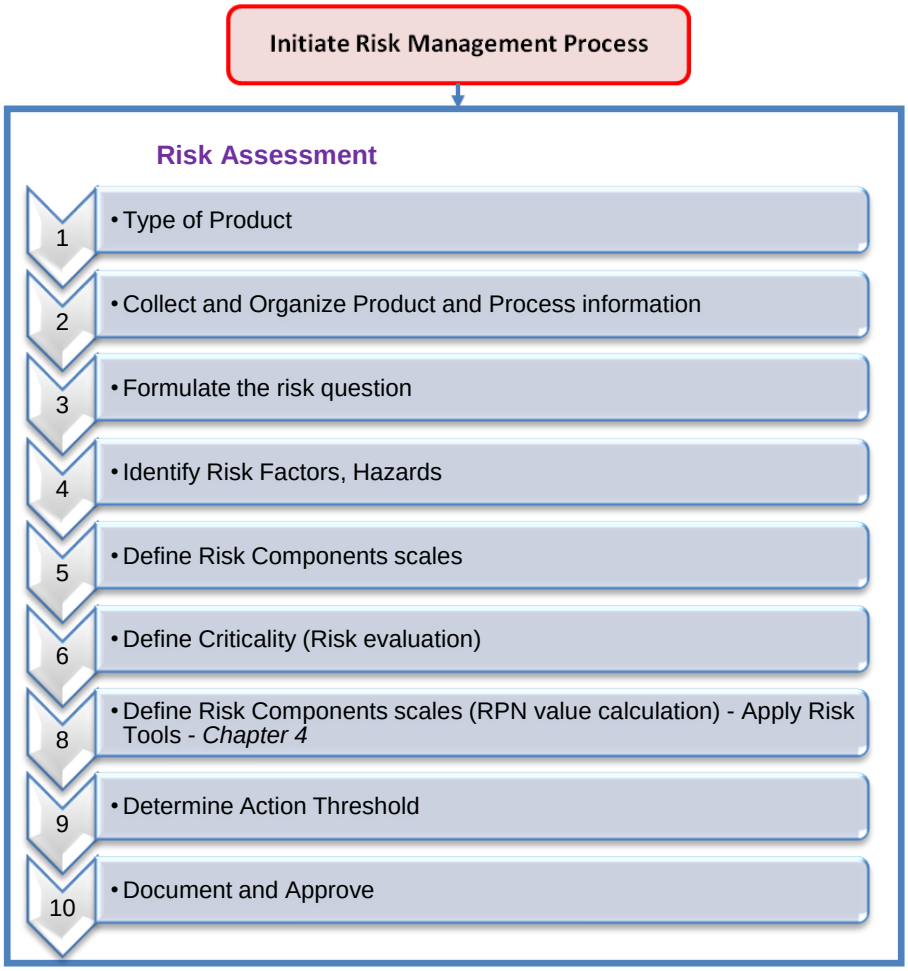
1) **Evaluation of System State of Control - Risk Assessment**
2) **Description of Process Controls and Process Characterization**
    a) **The sampling plan is adequate**
    b) **The system is stable**
    c) **The system is capable**
3) **Design space**
4) **Risk Reviewed by Quality and Risk Communication**
5) **Cleared for distribution**
6) **Continuous Product Verification**

Below are described in detail the activities as a guideline for an Process Performance qualification of Tech Transfer batches, New Products, Processes changes and Continuous process verification.

1) Evaluation of System State of Control - Risk Assessment

In order to make possible a risk approach for Process validation a general methodology was defined for Hikma Risk Assessments. This risk approach has the objective to improve the way the process is defined and also identifies crucial areas and/ or steps in the process, areas of risk and or hazard, and critical control points. Mainly this step should be followed for a new product development nevertheless an existent process (or part of the process) re-evaluation can also start at this stage (e.g. scale-up). Undoubtedly, products risk assessment is created for products`life.

Figure 48: Hikma 9 Steps Approach for Products Risk Assessment



Type of product

- Define Production line
- Evaluate Formulation
- Detail Manufacturing process
- Describe product materials compatibilities
- Evaluate sensitivities (heat, air, light)
- Define container closure

Collect and Organize Product and Process information

- Gathering relevant information, reviewing appropriate references and identifying assumptions
- Statistical tools (*Chapter 4*) can be used to organize information
- Define the boundaries of the QRM exercise – specific process step validation, all manufacturing process validation, investigation, scale-up process, new API source validation, ...)

Formulate the Risk Question

Starting point of the QRM exercise, high level statement outlines the issue and purpose for conducting the QRM exercise including risk factors, the scope of the issue and any related limits or constrains.

Identify Risk Factors, Hazards

This project phase combines technology with the experience of people to identify potential failure modes of the product or manufacturing process dependent on what is being validated.

Define Risks Components and scales

In terms of a QRM exercise to create a valuable schedule the following risk components scales (**Table 8**) were defined:

- **Severity of harm** – a measure of the possible consequences or degree of harm;
- **Probability of harm will occur** – frequency or likelihood of occurrence of the hazard;
- **Detection of risk** – the ability to discover or determine the existence, or presence of the hazard

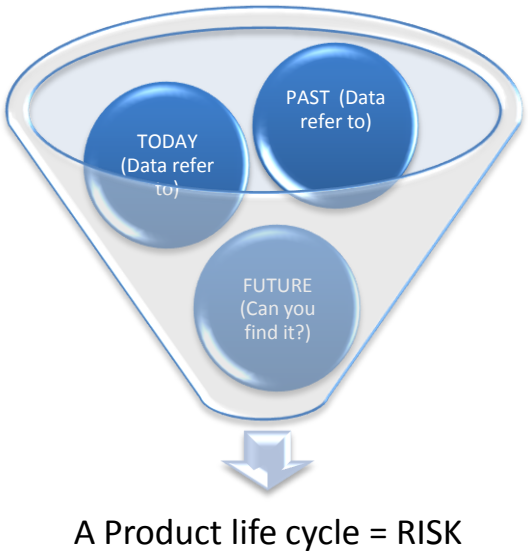


Figure 49: Detectability of risk over product lifecycle determined based on people experience.

Table 8: Key to construct the assessment tool for each product

Severity (S)	Scale definition
1	Effect does not have any impact on internal procedures or regulatory requirements. Effect has no impact on product quality.
2	Effect has minor impact on internal procedures and may result in minor regulatory observations. Effect has minor impact on product quality.
3	Effect has moderate impact on internal procedures and may result in regulatory observations. Effect has minor impact on product quality.
4	Effect has major impact on internal procedures and may result in regulatory observations. Effect has impact on product quality.
5	Effect may lead to critical regulatory observation and may result in product failure.
Occurrence (O)	**Scale definition**
1	Remote probability of occurrence. Occurence is rarely.
2	Low probability of occurance. Occurence is not frequent.
3	Moderate probability of occurence. Occurence is periodic.
4	High probability of occurence. Occurrence is frequent.
5	Very high probability of occurence. Certain to occur.
Detection (D)	**Scale definition**
1	Very high likelihood of detection. Current controls will almost certainly detect cause of failure.
2	High likelihood of detection. Current controls may not detect cause of failure.
3	Moderate likelihood of detection. Current controls may not detect cause of failure.
4	Low likelihood of detection. Current controls will most likely not detect cause of failure.
5	Remote likelihood of detection. Current controls will very likely not detect the cause of failure.

Define Criticality (Risk evaluation)

It compares the identified and analysed risk against given risk criteria. Risk evaluations consider the strength of evidence for Criticality and Detection.

Table 9: Calculation for Criticality

S x O	1	2	3	4	5
1	1	2	3	4	5
2	2	4	6	8	10
3	3	6	9	12	15
4	4	8	12	16	20
5	5	10	15	20	25

Determine Action Threshold

A level or value above which an action will take place and below it will not.

Define Risks Components scales

In order to facilitate the process validation study initiation a general tool for Hikma Risk Assessment was created (**Table 11**), where the main potential variations for an injectable product manufacturing are summarized. This tool can be applied to different products as the scores are attributed for severity, probability and detection (**Table 8**) dependent on each product and the risks impact on CQA. In addition the actions required based oon the obtained threshold are detailed for each risk.

This tool can be used to evaluate / study a specific process phase (as it is divided into sections) or the all manufacturing process of an injectable product. Since processes are not static over the product life also the critical aspects can change and/ or new risks might come into sight, and consequently this tool should be continuously optimized. Furthermore, the reports numbers for the studies relative to each product / vial / stopper / line should be added in where it is appropriate in order to facilitate the assess to relevant risk information on the table. This tool can be customized over the years in order to be more specific for each Hikma production line covering more items and also to be modified to new lines. Recently, new products with much specificity (extreme temperatures, low headspace oxygen, etc.) are being developed due to technological improvements ending in more complex manufacturing processes.

Table 10: Calculation of Risk Priority Number (RPN)

	D				
S x O	**1**	**2**	**3**	**4**	**5**
25	25	50	75	100	125
20	20	40	60	80	100
16	16	32	48	64	80
15	15	30	45	60	75
12	12	24	36	48	60
9	9	18	27	36	45
8	8	16	24	32	40
6	6	12	18	24	30
5	5	10	15	20	25
4	4	8	12	16	20
3	3	6	9	12	15
2	2	4	6	8	10
1	1	2	3	4	5

Table 11: Risk Assessment for Hikma Injectable Products – Critical Process Parameters

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
warehouse/ preparation for compounding	W1	Weighing of API	Incorrect weight.	Low or high assay results (OOS bulk IPC); batch failure.		Wrong calibration of the scales. Human error during weighing.		IPC assay (fill volume adjustment in order to compensate the difference on potency). Scales are calibrated daily. All weights are triple verified by both compounding operators and QA.		0	0	No RISK no further test is required	Comparation of Hikma CoA results with Supplier CoA results in order to confirm the results are aligned.
	W2	Weighing of Excipients	Incorrect weight.	Bulk solution IPC OOS. Finished Product OOS. Reduced stability.		Wrong calibration of the scales. Human error during weighing.		Scales are calibrated daily. All weights are double verified by both compounding operators and QA.		0	0	No RISK no further test is required	Controlled conditions to weight hygroscopy raw-materials. Low ventilation to weight light and fluffy powders.
	W3	Raw-Materials storage (sensitivities)	Raw-materials not overlayed with nitrogen; Not protected from light; not stored under appropriate conditions	Raw-materials degradation (high content of impurities) and decrease of potency		Human error (storage conditions not followed); If raw materials is not kept in the original container until production day.		All Raw-materials are sampled under laminar flow and the top of the containers overlayed with Nitrogen; here are specific instructions in SOPs and batch records		0	0	No RISK no further test is required	Raw-materials included in SOP compiling the conditions for the weighing
	W4	API calculation to adjust potency	Added amount of API is higher or lower than required	Low or high assay results (OOS bulk IPC); batch failure		API assay, Water content or Solvents wrongly reported in the CoA used for calculations; Human error in calculations		Calculation of API is double verified bedsore weighing and recorded in the MBR. All weights are double verified by both compounding operators and QA.		0	0	No RISK no further test is required	Formulas for API calculation adjustment revised by Quality Unit Director or QC Manager at the moment of Batch records approval
Compounding	C1	Initial WFI / oil / liquid excipient weighing in the compounding tank	Incorrect weight.	Low or high assay results (OOS bulk IPC); batch failure.		Wrong calibration of the scales. Human error during weighing.		Scales are calibrated daily. All weights are double verified by both compounding operators and QA.		0	0	No RISK no further test is required	N/A

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	C2	DO in bulk solution (or initial solution purged with filtered Nitrogen)	Oxygen content higher than x mg/ L	API degradation. Preservatives (if present) that reduce the reactive oxygen in solution are consumed immediately. Reduced product stability.		Oxygen sensor malfunction. Human errors (high mixing speed allow oxygen in the solution; tank not closed after purging)		Control of DO in solution using an oxygen sensor daily calibrated.		0	0	No RISK no further test is required	Oxygen sensitivity and stability studies for different headspace oxygen percentages.
	C3	Dissolution of API	Insufficient mixing time and/ or speed; or over mixing	Incomplete dissolution of API; Bulk solution does not need IPC specifications		Human error; incorrect visual evaluation of dissolution		Mixing speed in vortex is evaluated during all PPQ batches in order to validate a range. Samples are taken from the bottom for visual check of API dissolution.		0	0	No RISK no further test is required	Closely monitored during validation studies (time and mixed speed)
	C4	Foam formation during mixing for raw-materials dissolution / sparging with filtered nitrogen	Flow rate of nitrogen sparging is high or mixing speed is high.	Product (foam) comes out from the tank; high DO with no possibility to continue sparging; visual confirmation of raw-materials dissolution is impossible. Bulk IPC OOS,		Human error; insufficient monitoring of batch preparation		Products forming foam are compounded in bigger tanks size than the set batch size. Nitrogen overlay helps to control the foam.		0	0	No RISK no further test is required	Prior to PPQ confirm the possibility of bulk solution forms foam; and design the process with an appropriate tank size for compounding accordingly
	C5	Product light protection	tank entrance not closed or covered with aluminium foil between raw-materials addition	API degradation. Reduced product stability.		Human error.		Operators are trained in product specificities and sensibilities. No other controls are implemented.		0	0	No RISK no further test is required	Photostability studies.

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	C6	Dissolution of Excipients	Insufficient mixing time and/ or speed; or over mixing	Incomplete dissolution of API; Bulk solution does not meed IPC specifications		Human error; incorrect visual evaluation of dissolution.		Mixing speed in vortex is evaluated during all PPQ batches in order to validate a range. Samples are taken from the bottom.		0	0	No RISK no further test is required	Reference time for mixing of excipients in development report. Industrial mixing times and speeds for specific batch in specific tank detailed in Validation Report.
	C7	Preparation Holding time	Excessive hold time from the API addition to the end of compounding / beginning of lyophilisation cycle OR if volatile excipients in formulation (e.g. ethanol) long holding times for preparation will reduce their content in solution	Increase of impurities		Product is not stable for long time in liquid state. Human error, mechanical problem in the line can lead to exceeding the bulk holding time.		All critical times have to be studied and documented in the batch record. Solution is stored in sealed tank.		0	0	No RISK no further test is required	Maximum holding time between API addition and beginning of freezing phase to be evaluated for lyophilized products Or for liquid products - Maximum holding time between API addition and end of filling.
	C8	Heating or cooling the solution	Temperature above or below the set limits	Increase of impurities. Dissolution difficulties		Human error, mechanical problem (in chiller or heater)		Temperature limits for applicable steps are written in the batch records and are double check by 2 compouding operators.		0	0	No RISK no further test is required	Closely monitored during validation studies

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOx D*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	C9	pH adjustments	pH not in the required range	Reduced buffer capacity; Reduced stability		Human error, pH meter pH meter not correctly calibrated		pH meter is calibrated daily. pH specified in batch record and pH readings are double verified. After all adjustments QC confirm		0	0	No RISK no further test is required	Expected amount of pH adjustment solutions mentioned in Development report
	C10	Liquids excipients with high viscosity	Not totally transferred to preparation tank	Low or high assay (compromise the batch)		Human error		If these liquids are not weight directly in the preparation tank, there are other actions as mechanical removal with WFI or container wash with bulk solution from the compounding tank (if not removed with another organic solution)		0	0	No RISK no further test is required	Weighing procedures adjusted to different materials viscosities in order to reduce losses
	C11	Final Q.S.	Human error; balance malfunction	Low or high assay (compromise the batch)		Human error, scale malfunction		Balance is calibrated and verified prior to each compounding as per SOP. The Q.S. is double verified.		0	0	No RISK no further test is required	Quantify the water amount to be added to the final Q.S.
	C12	Tank Transfer	Product losses; Contamination; materials incompabilities	Bioburden OOS; High RS content		Human error.		All tanks are cleaned and sterilized using validated procedures. The compatible materials with product are described in the batch record. The tank holding time after CIP/SIP is qualified. The product holding time in the transference tank is validated for a certain time (can be up to 72 h).		0	0	No RISK no further test is required	Validation study for product transference. Bulk holding time in transference tank.

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	C13	Bulk Solution Sampling	Incompatibility with containers; Contamination; use of non-dedicated or disposable materials; incorrect sampling procedures; product oxidation	High results for related substances and low assay results; high bioburden; products cross contamination; assay OOS. Results not representative of bulk solution (false results). Batch failure.		Incorrect sampling procedures. Wrong sampling containers used. High headspace oxygen inside the sampling container that can react with the product.		Surfaces compatibility studies are made for Hikma products and requested for clients' products; Operators are trained in compounding GMPs every year; for oxygen sensitive products the sampling container has to be totally filled l no avoid headspace.		0	0	No RISK no further test is required	Batch sampled in different containers for compatibility surfaces studies.
Sterilization of equipment and materials	S1	Sterilization and Depyrogenation of glass containers	Cycle parameters not met.	Non sterile and pirogenic containers, broken containers.		Human error , mechanical problem, probes not calibrated.		Probes calibrated on annual basis; cycle specified in batch record and SOP, all documentation reviewed after sterilization. Sterilization cycle parameters validated for each type of vials.		0	0	No RISK no further test is required	Validation report for vials (size, moulded or tubular) sterilization/ depyrogenation in the tunnel
	S2	Sterilization of stoppers and machine parts	Materials are not sterilized utilizing the validated parameters (cycle and load configuration)	Not sterile stoppers / parts		Human error, mechanical problem		Probes calibrated on annual basis, cycle specified in batch record and SOP, all documentation/print outs/alarms reviewed after sterilization. Loads validated.		0	0	No RISK no further test is required	Report for Loads validation exists
Filtration	FT1	Filtration (and pre-filtration)	Filter non-integral	Filled product non sterile; High Bioburden results after pre-filter		Human error; faulty filter		Each filter has a "Certificate of test" from supplier. New filter used each production and pre- and post- integrity test are conducted before and after production, respectively.		0	0	No RISK no further test is required	Filter supplier Certificate of test (Bubble point test or diffusion flow test)

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
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	FT2	Filtration (and pre-filtration)	Filter non compatible with product	Low assay, high impurities		Materials not compatible with product; product conditions (temperature and pH) different from what is validated		The same filter membrane was used during R&D batches and stability is conforming. Filter validation studies performed with product, by filter supplier.		0	0	No RISK no further test is required	Supplier filter validation studies (Bacterial Challenge, Compatibility, Extractables)
	FT3	Final filtration	Filter clogging	Bulk solution not total filtered/ Low yield of filled units		Not appropriated filter size		Filterability studies performed.		0	0	No RISK no further test is required	Filterability studies
Aseptic Filling	FL1	Machine set-up Effect of filling equipment	Incompatibility of filling contact parts materials with the product leading to leachables and potential adverse reactions. Incorrect tubing, adverse reactions. Not filling under nitrogen/inert gas if the product is oxygen sensitive	Low assay and high impurities		Materials used during filling are not compatible with product. Human error / materials incompabilities		Tubing and equipment to be used is specified in the batch record. Surfaces incompatibilities studied during R&D batches. Equipment and materials are specified in the batch record. An initial flushing to the filling line is performed (if validated a specific volume to discard is described in the batch record). Surfaces compatibility studies are done for each product. The need of filling under nitrogen is also specified on the batch record.		0	0	No RISK no further test is required	Surfaces compatibility study. Oxygen sensitivity studies.

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOx D*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	FL2	Volume adjustments	Incorrect volume adjustment	-Product collapse during Lyophilisation process; mass and volume of product exceeding amount of solvent that can be removed during processing (overfill for lyophilized products: -Product , high assay result - Low assay result (under fill)		Improper control of filling vials / machine malfunction / wrong IPC balance calibration		Start of filling is confirmed by 3-10 vials within the limits. Weight checks during filling and visual inspections at the end of the process		0	0	No RISK no further test is required	Filling machine is capable of fill the product in the specific vial size within the specified volume limits PPQ for fill volume.
	FL3	Effect of filling process procedures	Routine filling interventions / Interventions due to any mechanical problem	non sterile product (safety and quality problem)		Operators not qualified in each intervention/ human error		Filling process is covered by media fill.		0	0	No RISK no further test is required	Media fill report covering the vial size and filling procedures/ interventions
	FL4	Filling line speed	fill volume variations	Extractable volume (if liquid) or Uniformity of content (if lyo) OOS; batch failure.		Fill line speed not studies or wrong parameters set in the batch record.		Acceptable proven filling speed range is documented in the batch record.		0	0	No RISK no further test is required	Acceptable Proven Filling speed range study

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5** [1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5** [1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5** [1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	FL5	Effect of Filling stoppages	Increase time for product contact with surfaces and temperature variations of product inside the filling machine	Low assay, high impurities		Maintenance interventions due to technical problems;		Actions to be taken after a stoppage stated on the MBR		0	0	No RISK no further test is required	Impact of stoppages up to 2 hours study
Lyophilisation	LY1	Evacuation	Vials completely closed (not partially stoppered)	Potential for collapse of product		Stoppering failure during filling / human error		Visual control by filling operators during the entire filling		0	0	No RISK no further test is required	Special training to filling operators in the difference of filling a liquid and a lyo product
	LY2		Shelf temperature too high	Potential for partial collapse on top of product		Malfunction of shelf temperature control system		Calibration of temperature sensors and control loop PM of temperature control components			0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.
	LY3		Shelf temperature set point too high	Potential for partial collapse on top of product		Selection of incorrect lyophilisation program		Supervisor training and batch record / SOP control (lyophilizer alarms)		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
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	LY4		Chamber pressure too high	Potential for collapse on top of product		Excessive frost build-up on shelves		Loading area humidity control and batch record limits (if any) on duration of loading		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.
	LY5		Pressure set-point incorrect	Potential for collapse on top of product		Water from sterilization cycle. Selection of incorrect lyophilisation program		PM of unit and visual detection by operator. Operator training and batch record control.		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.
	LY6	Product Primary drying	Shelf ramp to primary drying too fast	Melt back or collapse		Malfunction of shelf temperature control system.		Calibration of temperature sensors and control loop PM of temperature control components		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.
	LY7		Shelf temperature too high	Rapid drying, potential for product collapse		Selection of incorrect lyophilisation program; Malfunction of shelf temperature control system		Operator training and batch record / SOP control; Calibration of temperature sensors and control loop PM of temperature control components.		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
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	LY8		Shelf temperature too low	Slow drying, potential for incomplete primary drying and collapse in transition to secondary drying		Malfunction of shelf temperature control system.		Calibration of temperature sensors and control loop PM of temperature control components		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.
	LY9		Shelf temperature set point too low	Slow drying, potential for incomplete primary drying and collapse in transition to secondary drying		Selection of incorrect lyophilisation program		Operator training and batch record / SOP control.		0	0	No RISK no further test is required	R&D lyophilisation cycle development; Executed lyo cycles prints-outs evaluated versus approved lyophilization cycle. Lyophilization cycle alarms evaluated.
	LY10		Step duration too short	Product collapse or excessive moisture		Selection of incorrect lyophilisation program; Malfunction of timer system; Trays used to dry product warped or changed; Heat transfer characteristics of scaled -up lyophilizer different from those of previous unit; Less extraneous heat available compared to previous unit; Larger load, less edge effects.		Operator training and batch record / SOP control; Periodic requalification of microprocessor controller; Batch record control, PM on tray, inspection of trays during process; Qualification of lyophilizers.		0	0	No RISK no further test is required	Consider sublimation studies to compare sublimation rates in scale-up and previous lyophilizer, cycle modification.

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
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	LY11		Chamber pressure too high	Potential for product collapse (during primary drying) high moisture		Selection of incorrect lyophilisation program; Malfunction of chamber pressure control system; Different pressure-sensor operating characteristics than those used in previous lyophilizer; Condenser capacity insufficient		Operator training and batch record / SOP control; Calibration of pressure sensors and control loop PM of pressure control components; Equipment design specifications, qualification studies.		0	0	No RISK no further test is required	Compare operating characteristics of lyophilizers as part of technology transfer
	LY12		Chamber pressure control too low	Potential for incomplete primary drying (collapse in transition to secondary drying)		Selection of incorrect lyophilisation program; Malfunction of chamber pressure control system; Different pressure-sensor operating characteristics than those used in previous lyophilizer.		Operator training and batch record / SOP control; Calibration of pressure sensors and control loop PM of pressure control components.		0	0	No RISK no further test is required	Compare operating characteristics of lyophilizers as part of technology transfer
	LY13	Product secondary drying	Ramp to secondary drying too severe	Potential product collapse, excessive heating for partially wet cake.		Selection of incorrect lyophilisation program; Malfunction of shelf temperature control system; Condenser capacity insufficient.		Operator training and batch record / SOP control; Calibration of pressure sensors and control loop PM of pressure control components; Equipment design specifications, IQ/OQ studies.		0	0	No RISK no further test is required	Additional Controls / Tests to be implemented during Process Validation

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
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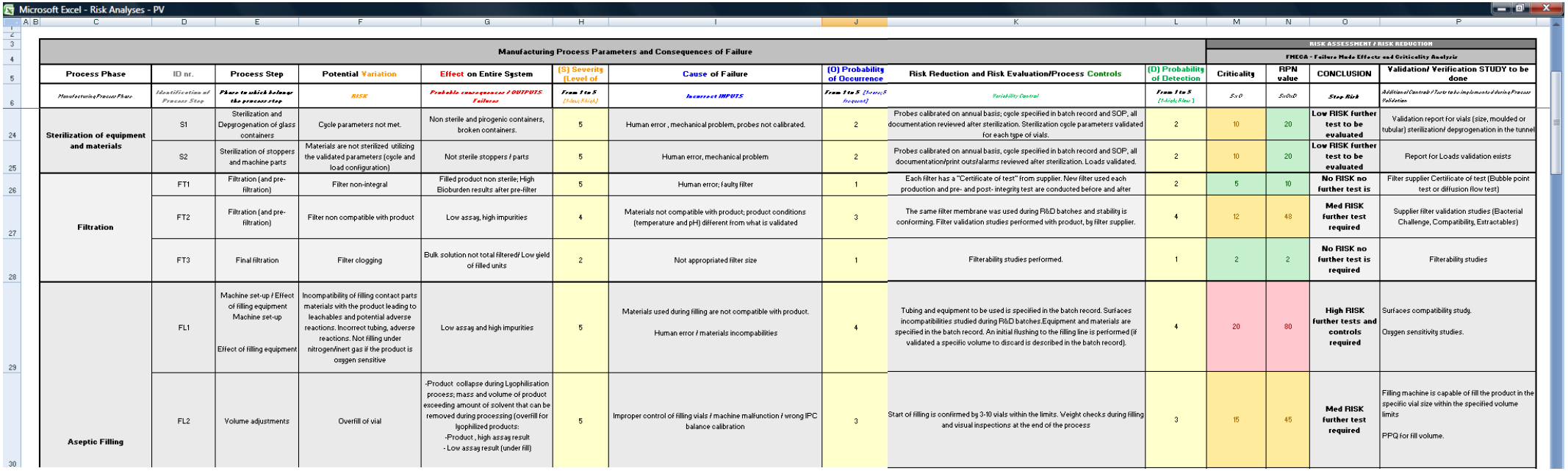
	LY14	Lyophilizer PLC error	High water content, high impurities and non-conforming cake	Batch failure		Lyophilizers have alarms. Verification of lyo cycle is done for pressure, temperature and time by supervisors along the cycle duration. Key people are informed if any		Lyophilizers have alarms. Verification of lyo cycle is done for pressure, temperature and time by supervisors along the cycle duration. Key people are informed if any alarm occur during the cycle. The cycle print out is evaluated at the end of the cycle.		0	0	No RISK no further test is required	Applicable alarms suggested in R&D lyophilisation cycle development report.
Sealing	SE1	capping vials	Poor sealing; Not properly seated stoppers	Non integral-vial.		Human error		Capper set-up per component configuration. IPC performed during capping		0	0	No RISK no further test is required	Container/closure integrity studies.
Terminal sterilization	TS1	Batch Sterilization	Product degradation	Results OOS		Autoclave malfunction		During PPQ execution, after one batch filling, one tray of the product is sterilized twice. The rest of the batch is going to be sterilized according to approved product conditions.Samples are placed on stability after TS.		0	0	No RISK no further test is required	R&D team studies the impact on Terminal sterilization on the product.
100 % Particles inspection	I1	Inspection	Particles	Batch failure		Product degradation / Process related		Automatic Inspection is performed in all batches		0	0	No RISK no further test is required	All PPQ batches are inspected and after 10 batches alert and action limits are set.
Product storage	STO1	Product storage from inspection and packaging to shipment.	Excessive exposure to light, temperature above or below the recommended range	Reduced stability of product.		Human error, failure to comply with storage conditions.		Training of operators, instructions documented in batch record. Storage conditions verified in validation.		0	0	No RISK no further test is required	Stability studies. Photostability studies.

Also risk mitigation can simply reveal the most critical process steps that might impact CQA, as well as other tools described under Chapter 4 – PARAMETERS AND METHODS – Quality Risk Management Tools.**Figure 50** exemplifies the use of this tool for an injectable product for a filtration process of a generic Hikma manufacturing process.

Figure 50: Example of a risk assessment to be used in a process validation plan

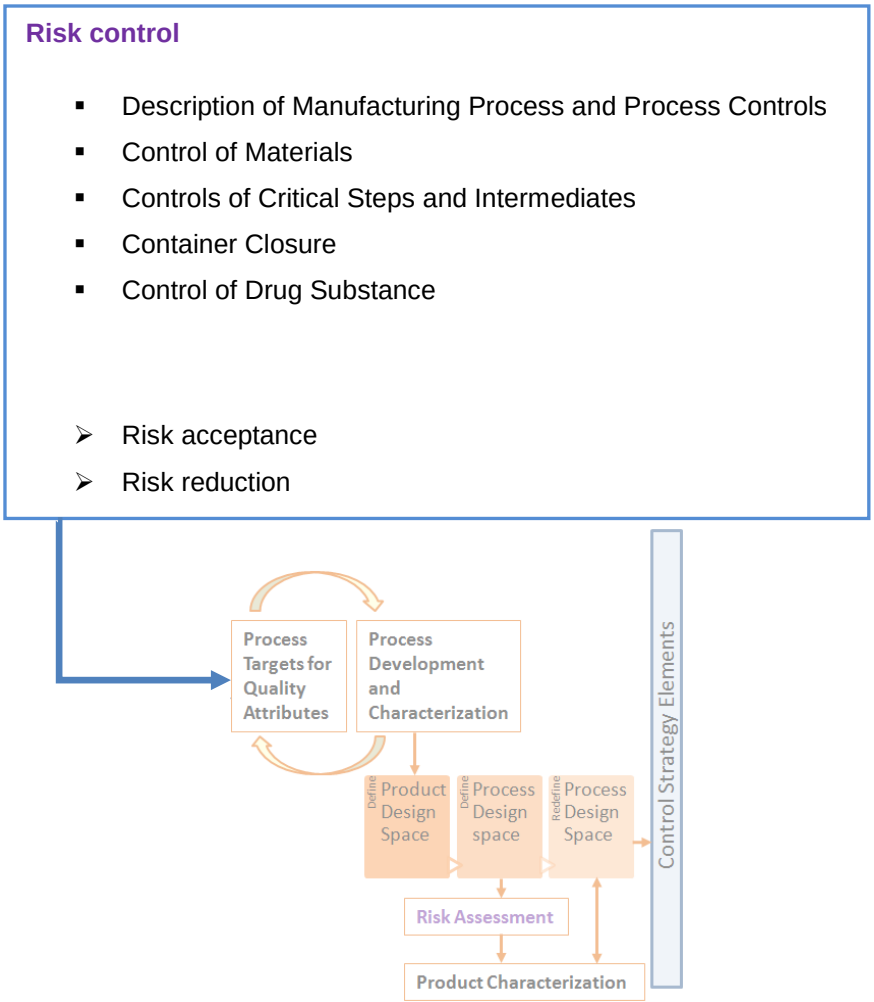


Microsoft Excel - Risk Analyses - PV

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	*RISK*	***Probable consequences / OUTPUTS Failures***	***From 1 to 5***	***Incorrect INPUTS***	***From 1 to 5***	*Variability Control*	***From 1 to 5***	*5 x O*	*5 x O x D*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
Sterilization of equipment and materials	S1	Sterilization and Depyrogenation of glass containers	Cycle parameters not met.	Non sterile and pirogenic containers, broken containers.	5	Human error , mechanical problem, probes not calibrated.	2	Probes calibrated on annual basis; cycle specified in batch record and SOP, all documentation reviewed after sterilization. Sterilization cycle parameters validated for each type of vials.	2	10	20	**Low RISK further test to be evaluated**	Validation report for vials (size, moulded or tubular) sterilization/ depyrogenation in the tunnel
	S2	Sterilization of stoppers and machine parts	Materials are not sterilized utilizing the validated parameters (cycle and load configuration)	Not sterile stoppers / parts	5	Human error, mechanical problem	2	Probes calibrated on annual basis, cycle specified in batch record and SOP, all documentation/print outs/alarms reviewed after sterilization. Loads validated.	2	10	20	**Low RISK further test to be evaluated**	Report for Loads validation exists
Filtration	FT1	Filtration (and pre-filtration)	Filter non-integral	Filled product non sterile; High Bioburden results after pre-filter	5	Human error; faulty filter	1	Each filter has a "Certificate of test" from supplier. New filter used each production and pre- and post- integrity test are conducted before and after	2	5	10	**No RISK no further test is**	Filter supplier Certificate of test (Bubble point test or diffusion flow test)
	FT2	Filtration (and pre-filtration)	Filter non compatible with product	Low assay, high impurities	4	Materials not compatible with product; product conditions (temperature and pH) different from what is validated	3	The same filter membrane was used during R&D batches and stability is conforming. Filter validation studies performed with product, by filter supplier.	4	12	48	**Med RISK further test required**	Supplier filter validation studies (Bacterial Challenge, Compatibility, Extractables)
	FT3	Final filtration	Filter clogging	Bulk solution not total filtered/ Low yield of filled units	2	Not appropriated filter size	1	Filterability studies performed.	1	2	2	**No RISK no further test is required**	Filterability studies
Aseptic Filling	FL1	Machine set-up / Effect of filling equipment Machine set-up Effect of filling equipment	Incompatibility of filling contact parts materials with the product leading to leachables and potential adverse reactions. Incorrect tubing, adverse reactions. Not filling under nitrogen/inert gas if the product is oxygen sensitive	Low assay and high impurities	5	Materials used during filling are not compatible with product. Human error / materials incompabilities	4	Tubing and equipment to be used is specified in the batch record. Surfaces incompatibilities studied during R&D batches.Equipment and materials are specified in the batch record. An initial flushing to the filling line is performed (if validated a specific volume to discard is described in the batch record).	4	20	80	**High RISK further tests and controls required**	Surfaces compatibility study. Oxygen sensitivity studies.
	FL2	Volume adjustments	Overfill of vial	-Product collapse during Lyophilisation process; mass and volume of product exceeding amount of solvent that can be removed during processing (overfill for lyophilized products: -Product , high assay result - Low assay result (under fill)	5	Improper control of filling vials / machine malfunction / wrong IPC balance calibration	3	Start of filling is confirmed by 3-10 vials within the limits. Weight checks during filling and visual inspections at the end of the process	3	15	45	**Med RISK further test required**	Filling machine is capable of fill the product in the specific vial size within the specified volume limits PPQ for fill volume.

2) Description of Process Controls and Process Characterization

The information provided on the control strategy should include detailed descriptions of the individual elements of the control strategy plus, when appropriate, a summary of the overall drug substance control strategy. Particularly at the time that precedes the Process Performance qualification, it is important to describe in a detailed manner the process controls.



During Product lifecycle this state of control is ensured also by Process Design space verification. In PV Guidance from 2011 it is stated "*We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used measuring and evaluating* ***process stability*** *and* ***process capability***".

a. **The sampling plan is adequate** (in-process controls are covering the CQA)

The process validation sampling plan should be adequate to demonstrate sufficient statistical confidence of quality. One of the appropriate methodologies to design and analyse the process validation is a risk assessment tool (**Table 11**).

During PPQ the number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis since it is related with a particular attribute under examination.

- Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to ensure that batches of drug products meet each appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall included appropriate acceptance levels and/ or appropriate rejection levels.
- Valid in-process specifications for such characteristics shall be consistent and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.
- Examination and testing of samples shall assure that the drug product and in process material conform to specification.
- Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.

b. **The system is capable**

- The lower bound of CPK confidence interval (Figure 23 and Figure 24) should be evaluated (tied to the adequacy of sampling plan)
- Evaluate the criteria to analyse the process data
    - Expected data.

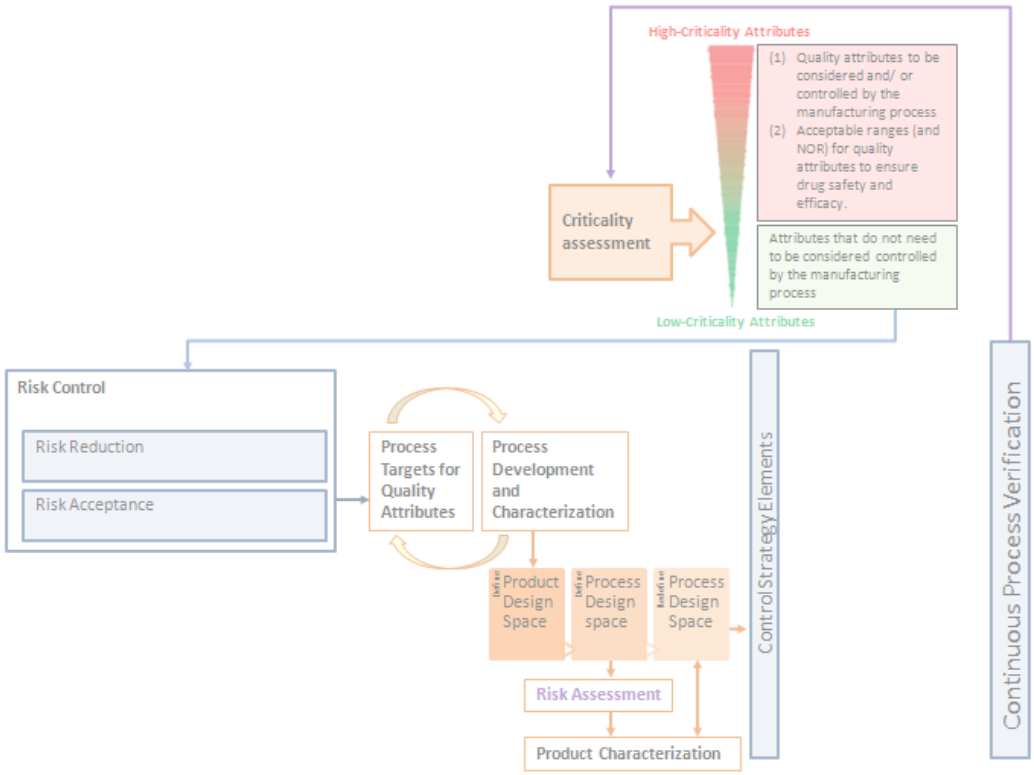
- If results are transformed, confirm if the specifications were transformed accordingly.
- Analyse data collected under operating conditions in order confirm process stability.

- *Question:* Can the process consistently make product that meets specifications?
- *Commonly used Statistical Tool:* Process Capability Studies
- *Targets:*
  - The demonstrated CPK ensures that Critical Quality Attributes (CQAs) are consistently met;
  - The CPK meets requirements of other steps in the process, particularly for in process data;
  - Remember, "The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination".

c. The system is stable

- *Question:* Can the process consistently make product that meets specifications?
- *Commonly used Statistical Tool:* Control Charts.
- Contrasting capability studies, time is taken into consideration.
- *Targets:*
  - The system is stable under controlled conditions;
  - Activities are performed during commercial manufacturing to continually assure that the process remains in state of control;
  - Control limits do not exceed CQA specifications;
  - The variation is constant over the time;
  - As before, "The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination".
- *Points for consideration:*
  - Does the system ensure consistent product, even with varying inputs?
  - Do finished attributes "drift" within specifications, or are they stable over time?
  - Is it a natural variation or special cause variation?
  - Do you see acceptable time based variation both within batches and between batches?

3) Design space (statistical tools and risk assessment)



The figure above (part of Hikma QRM approach **Figure 47**) gives a high level of Quality by Design approach integrated in Risk approach. Knowledge of the quality target profile, a dynamic summary of the characteristics of a product to ensure the desired quality will drive the establishment of an adequate product specification, which will then lead process development and routine process improvements. The first criticality assessment goal is to brainstorm and document the rational through which variables should be studied in order to drive validation activities in a lean manner. To do this, it is necessary to prioritise the variables that may impact product CQAs throught the process, based on the perception of criticality using prior knowledge and past experience to quantify the impact.

During the stage of process development and scaling-up, Design of Space approach may be useful to quantify the link between the CQA and CPP and or CMA by means of statistical tools. Establishing and quantifying this relationship will constitute the bases for the design space, a multi-dimensional space of input variables that provides assurance of quality.

At this stage the process and the product should both be well characterised. While the design space will identify the feasible space, the normal operating ranges (NOR) should also be defined, i.e. the preferred operating spaces, considering performance aspects of the process, such as operational costs and process capability.

Here, a formal risk assessment tool is applied, linkin process development and manufacturing. One possible methodology to apply is FMECA (e.g. **Table 11**) listing

again all possible failure modes that may occur when in commercial manufacturing. Then, the potential effects related with failure are listed. For such a purpose, actions are identified to find and eliminate potential causes, potential failure modes and effects or to increase the level of detection.

The output of the risk assessment will feed the criticality analysis, where process parameters and material attributes are classified as critical or non-critical based on their impact on the final product`s CQAs. Critical parameters should be monitored and controlled to ensure that the process yields product with the desired quality.

The level of effort in controlling a critical parameter should reflect not only the FMEA output, but should also take into consideration other aspects, such as the magnitude of the effect (sensitivity to changes of the parameter value), the location of the NOR relative to the design space, the closeness of the design space to the edge of failure and the robustness of the process with regard to those parameters, translated into the process capability index.

The criticality will be a key driver for defining the process control strategy, through which the process will be kept in control throughout its lifecycle. This strategy should target the control of CMAs and CPPs to assure operation inside the design space and should also drive the continuous improvement and optimization of the process.

Trending tools – like control charts and process capability analisys – and investigational methods, such as multivariate analysis, may flag special and common causes of variation coming from variability not addressed during development and can quantify the impact on CQAs, increasing process knowledge. Process changes driven by the continuous improvement programme can be implemented following adequate change control procedures.

4) Risk Reviewed by Quality and Risk Communication

Address the need to revisit the risk assessment at a point in the future to take into account any new information/ experience

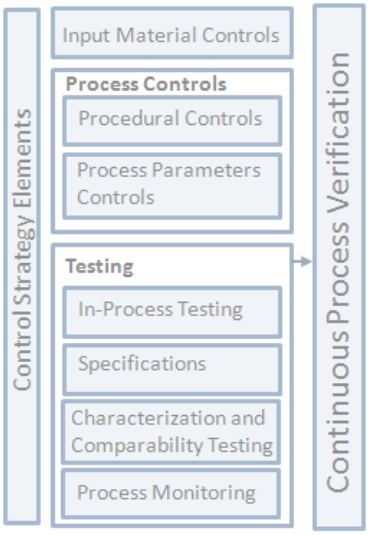
- Determine an appropriate frequently
- Purpose – what items will be reviewed
- Communicating information with key groups
- Understanding our risks and conveying them to others

5) Cleared for distribution

A Process Validation is the collection and evaluation of data, from the process designed stage and continuing through commercial production, which ensure that the manufacturing

process including equipment, building, personnel and materials is capable of achieving the intended results on a consistent and continuous basis (Guidance for Industry - Process Validation: General Principles and Practices, January 2011).

6) Continuous Product Verification



- Every batch manufactured provides more data (also see *Section 2.4.3 - Stage 3: Continued Process Verification (CPV)*);
- With more data, enhance process and product understanding;
- It is the Hikma`s responsibility to update the following accordingly:
  - Specifications
  - In process or manufacturing controls
  - Sampling plans

In order to assure that the process remains in a state of control (the validated state) during commercial manufacture, a robust system is required for detecting unplanned departures (drift) from the designed process, and there should be a strong emphasis on the use of statistically trended data, which should also be reviewed in a timely manner by trained personnel.

The development of a Data Collection Plan can be written ensuring that the information collected can verify that the critical quality attributes are being controlled throughout the process. The quality unit should evaluate this data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions with production personnel.

5.5 HIKMA CASE STUDIES – Risk Approach Implementation

This chapter aims to give a general idea about simple concepts to assess products` risk framework and to elucidate the use of Hikma Quality Risk Management approach for types of Hikma injectable products.

5.5.1 Aqueous solutions

During monitoring of bulk solution IPC for a liquid product it was verified that the obtained ascorbic acid assay result was consistently in low end, between 0.63 and 065 mg/ mL, while the limits were 0.62 – 0.98 mg/ mL (70 – 110 %). Also pH results seem to follow a tendency, but in an inverse manner, i.e. when the ascorbic acid assay was lower, the pH was higher. The product formulation is API, water, Ascorbic Acid and NaOH used for pH adjustment. Ascorbic acid is added to the formulation in a concentration of 0.89 mg/ mL (with no overage). Due to the fact that a considerable quantity of ascorbic acid is lost until the end of bulk preparation, a mitigation process was started and the chosen method was RAMM (described under *Section 4.5.3 - Risk Analysis and Mitigation Matrix (RAMM)*).

RAMM method will clarify in which direction the process parameters impact CQAs and which quantity of these parameters affects the CQAs are critical for manufacturing excellence. And this understanding can be used to optimize the process, increase ascorbic acid and consequently end up with a more robust process or add appropriate control measures to adjust process to make on target product.

Stage 1 – Team and Knowledge – The process was considered since materials weights and storage until the IPC sample is analysed. In total, more than 10 batches were initially supervised (before any action to control potential risk of ascorbic acid OOS assay) and ascorbic acid was also monitored to understand how process is run on a daily basis. Ascorbic Acid molecule properties were studied in order to collect information for risk analysis. Summing up Ascorbic acid has pKa values of 4.2 and 11.6. As a mild reducing agent, ascorbic acid degrades upon exposure to air, converting the oxygen to water. The redox reaction is accelerated by the presence of **metal ions** and **light**. It can be oxidized by one electron to a radical state or doubly oxidized to the stable form called dehydroascorbic acid.

Stage 2 – Identifying the CQAs – The desired CQAs are in this case the ascorbic acid assay, pH and density of the intermediate product - bulk solution.

- Higher Criticality is Ascorbic Acid Assay and it should be the focus of the risk assessment; therefore its importance was scored with **9.**
- Medium Criticality is pH (limits pH 8.5 – 9.1) as there was a possibility to contribute for the variation in study; it was scored with **3.**
- Low criticality is Density of bulk solution (1.0094 – 1.0196 g/ cm^3), anyhow it is part of In-process-controls for the bulk solution and it should be the focus of the risk assessment; therefore its importance was scored with **9.**

Stage 3 – Definition the Process Steps – Weighing of raw-materials and bulk solution manufacturing.

Stage 4 – Definition of Process and Material – The process steps were broken down into process parameters.

Stage 5 – RAMM construction and Scores – The RAMM uses a matrix of process input factors and quality attributes to assess risk and impact (**Table 12**). Some of Process became critical process parameters and other important parameters.

Likewise, the matrix can be filtered to determine which process step or input factors had the greatest impact on a particular attribute.

Table 12: Risk of citric acid losses during compounding mitigation

		Relative importance of CQA (Bulk IPC)	**9**	**3**	**1**	
Process step	**Class**	**Process Parameters**	**Assay (Citric acid) IPC**	**pH**	**Density**	**TOTAL**
Weighing Raw-materials	Procedure 1	Weigh API, Ascorbic Acid and HCl	1	1	1	1
Weighing Raw-materials	Procedure 2	Ascorbic Acid batch time since the first time container was opened (contact with light and oxygen)	3	1	1	3
Compounding	Personal 1	Equipment cleaning	1	1	1	1
Compounding	Procedure 3	Prepare HCl 1 N solution for pH adjustment	3	9	1	27
Compounding	Procedure 4	WFI addition	1	1	1	1

		Relative importance of CQA (Bulk IPC)	**9**	**3**	**1**	
Process step	**Class**	**Process Parameters**	**Assay (Citric acid) IPC**	**pH**	**Density**	**TOTAL**
Compounding	Procedure 5	WFI sparging with nitrogen	9	1	1	9
Compounding	Procedure 6	Ascorbic acid addition	9	9	1	81
Compounding	Procedure 7	1st pH adjustment (6.8 – 7.2) (WFI+ Ascorbic Acid)	9	9	1	81
Compounding	Procedure 8	1st API portion addition	1	1	3	3
Compounding	Procedure 9	2nd pH adjustment (WFI + API)	9	9	1	81
Compounding	Procedure 10	2nd API portion addition	1	1	3	3
Compounding	Procedure 11	3nd pH adjustment (time and mixing speed variable)	9	9	1	81
Compounding	Procedure 12	3nd API portion addition	1	1	3	3
Compounding	Procedure 13	4nd pH adjustment (time and mixing speed variable)	9	9	1	81
Compounding	Personal 14	Quantities added of NaOH at once				
Compounding	Procedure 15	Solution sparging with nitrogen	9	1	1	9
Compounding	Procedure 16	Bulk solution final volume	1	3	9	27
Sampling	Procedure 17	Sampling overlaid with nitrogen	9	1	1	9

The above matrix related the **CQA – <u>Ascorbic acid assay</u>** – with most **CPPs** as **<u>nitrogen sparging</u>** and **<u>pH adjustments</u>**. At this stage the RAMM can be sorted and filtered so that process inputs can be assessed by their impact on a specific response, by the interim process step, or for their overall impact on the entire process.

The process procedure was revisited with particular attention to nitrogen sparging steps and pH adjustments. The following <u>risk observations</u> were made:

- WFI is purged with nitrogen until Dissolved Oxygen (DO) ≤ 0.5 ppm, and only after Q.S. the bulk solution is again purged until DO ≤ 0.5 ppm;

- After ascorbic acid addition and until final Q.S. the preparation has no steps to perform nitrogen purging;

- During agitation/ dissolution of ascorbic acid in the preparation container (opened container) the DO increases quickly for more than 3 ppm and continues to increase during the API additions and the adjustments;

- During addition and dissolution of the 4 API portions and pH adjustments to pH 9.0, which takes around 1 hour, the preparation container is kept opened and the mixing has to be strong in order to dissolve the API leading to incorporation of air into the solution; during these steps there is no nitrogen overlaying;

- After last step of nitrogen purging to achieve DO ≤ 0.5 ppm, the nitrogen is turned off and the samples are collected while the solution is mixed leading again to incorporation of air into the solution;

- WFI to bring the volume to 98 % and then to 100 % is not previously sparged with nitrogen;

- No nitrogen overlaying is performed to the sampling containers;

- Bulk solution is not protected from light during compounding.

- The pH during adjustments after API addition increase for a small instant to pH 12 [one pka of ascorbic acid is 11.6]; immediately after the pH decreases while the API (acidic) is dissolving. API dissolves at approximately pH 9.00.

<u>Improvements were immediately implemented to the compounding process, as follows:</u>

- Additional step for purging the solution with nitrogen after ascorbic acid addition (and during pH adjustment to 6.8 – 7.2) until just before API addition;
- Overlaying the bulk solution with nitrogen during all four pH adjustments after API addition;
- WFI to bring the volume to 98 % and then to 100 % is previously sparged with nitrogen;
- After final purging step (after Q.S. and final homogenization) there are no advantage in keep mixing the solution (the solution is homogenous), the samples should be collected without agitation;
- Due to the impossibility of overlaying the sampling bottles with nitrogen, the containers should be filled until the top and in this way avoid oxygen headspace that can react with ascorbic acid;

- pH was kept under 9.5 during all pH adjustments; fixed portions (600 – 800 mL) of NaOH 1M solution have to be added slowly to the solution ;
- Agitation speed is controlled in order to be enough to achieve proper dissolution but not too vigorous to allow high oxygen incorporation into the solution;
- While waiting IPC results the solution is overlaid with nitrogen and the container sealed.

The obtained results for ascorbic acid assay, after the implementation of these controls and procedures into the compounding process, were between 0.82 – 0.84 mg/ mL (IPC specification 0.62 – 0.98 mg/ mL).

5.5.2 Oils

During a manufacturing campaign for three batches of an oil basis product at Hikma, differences in terms of API assay were found in bulk solution IPC. The results were within specification but the drift inter-batches predict some uncontrolled parameter. The main focus of process verification was the compounding of bulk solution and the assays of all batches compounded before in order to distinguish any trend (recently or since the product was commercialized).

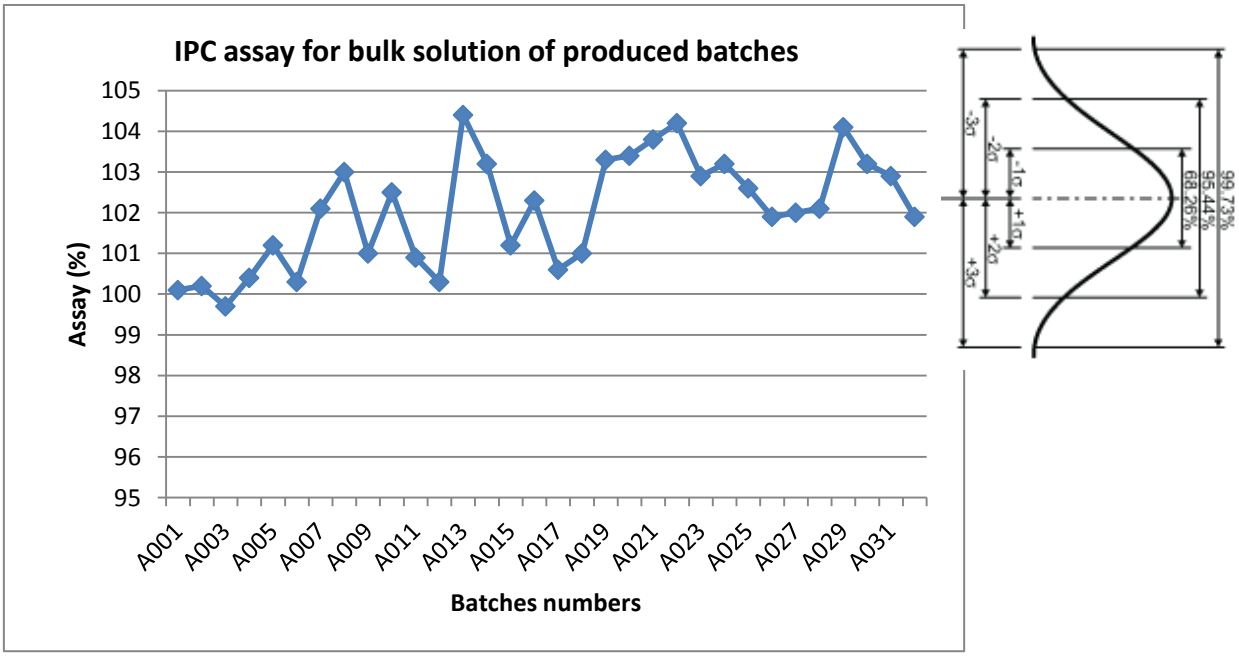


Figure 51: IPC assay for bulk solution of produced batches for an oil basis product.

Evaluating the above graphic that plots the data for IPC API assay results for 35 batches, no trend was observed. The variation was considered controlled since has a consistent pattern over time and the process seems to be operating within the bounds of the control limits of 95.0 % to 105.0 %. However, the Gass Curve is dislocated for the upper limits as the average is 102.1 %. This average limit indicates that some procedure or parameter could be working randomly. An investigation was iniciated and Hikma risk assessment (*Appendix* **Table-A 1**) was applied for weighing materials process step and compounding process step.

Figure 52: Hikma risk assessment tool applied for this Oil case – Priority RISK: Transfer liquid RM with high viscosity into the preparation tank – "High RISK further tests and controls required"

	imeters and Consequences of Failure				RISK ASSESSMENT / RISK REDUCTION FMEGA - Failure Mode Effects and Criticality Analysis			
5	Cause of Failure	(O) Probability of Occurrence	Risk Reduction and Risk Evaluation/Process Controls	(D) Probability of Detection	Criticality	RPN value	CONCLUSION	Validation/ Verification STUDY to be done
6	Incorrect INPUTS	From 1 to 5 [1=rare; 5 frequent]	Variability Control	From 1 to 5 [1=high; 5=no]	S x O	S x O x D	Step Risk	Additional Controls/ Tests to be implemented during Process Validation
12	Oxygen sensor malfunction. Human errors (high mixing speed allow oxygen in the solution; tank not closed after purging)	1	Control of DO in solution using an oxygen sensor daily calibrated.	1	1	1	**No RISK no further test is required**	Oxygen sensitivity and stability studies for different headspace oxygen percentages.
13	Human error; incorrect visual evaluation of dissolution	3	Mixing speed in vortex is evaluated during all PPQ batches in order to validate a range. Samples are taken from the bottom for visual check of API dissolution.	4	15	60	**Med RISK further test required**	Closely monitored during validation studies (time and mixed speed)
14	Human error; insufficient monitoring of batch preparation	1	Products forming foam are compounded in bigger tanks size than the set batch size. Nitrogen overlay helps to control the foam.	1	1	1	**No RISK no further test is required**	Prior to PPQ confirm the possibility of bulk solution forms foam; and design the process with an appropriate tank size for compounding accordingly
15	Human error.	2	Operators are trained in product specificities and sensibilities. No other controls are implemented.	2	2	4	**No RISK no further test is required**	Photostability studies.
16	Human error; incorrect visual evaluation of dissolution.	4	Mixing speed in vortex is evaluated during all PPQ batches in order to validate a range. Samples are taken from the bottom.	4	16	64	**Med RISK further test required**	Reference time for mixing of excipients in development report. Industrial mixing times and speeds for specific batch in specific tank detailed in Validation Report.
17	Product is not stable for long time in liquid state. Human error, mechanical problem in the line can lead to exceeding the bulk holding time.	2	All critical times have to be studied and documented in the batch record. Solution is stored in sealed tank.	1	6	6	**No RISK no further test is required**	Maximum holding time between API addition and beginning of freezing phase to be evaluated for lyophilized products
18	Human error, mechanical problem (in chiller or heater)	1	Temperature limits for applicable steps are written in the batch records and are double check by 2 compouding operators.	1	4		No RISK no further test is required	Or for liquid products - Maximum holding time between API addition and end of filling.
19	Human error	5	If these liquids are not weight directly in the preparation tank, there are other actions as mechanical removal with \rFI or container wash with bulk solution from the compounding tank (if not removed with another organic solution)	5	25	125	**High RISK further tests and controls required**	Weighing procedures adjusted to different materials viscosities in order to reduce losses
20	Human error, scale malfunction	2	Balance is calibrated and verified prior to each compounding as per SOP. The Q.S. is double verified.	1	8	8	**further test is**	Adjusting the water amount to be added to the final Q.S.
21	Human error.	4	All tanks are cleaned and sterilized using validated procedures. The compatible materials with product are described in the batch record. The tank holding time after CIP/SIP is qualified. The product holding time in the transference tank is validated for a certain time (can be up to 72 h).	4	12	48	**Med RISK further test required**	Validation study for product transference. Bulk holding time in transference tank.

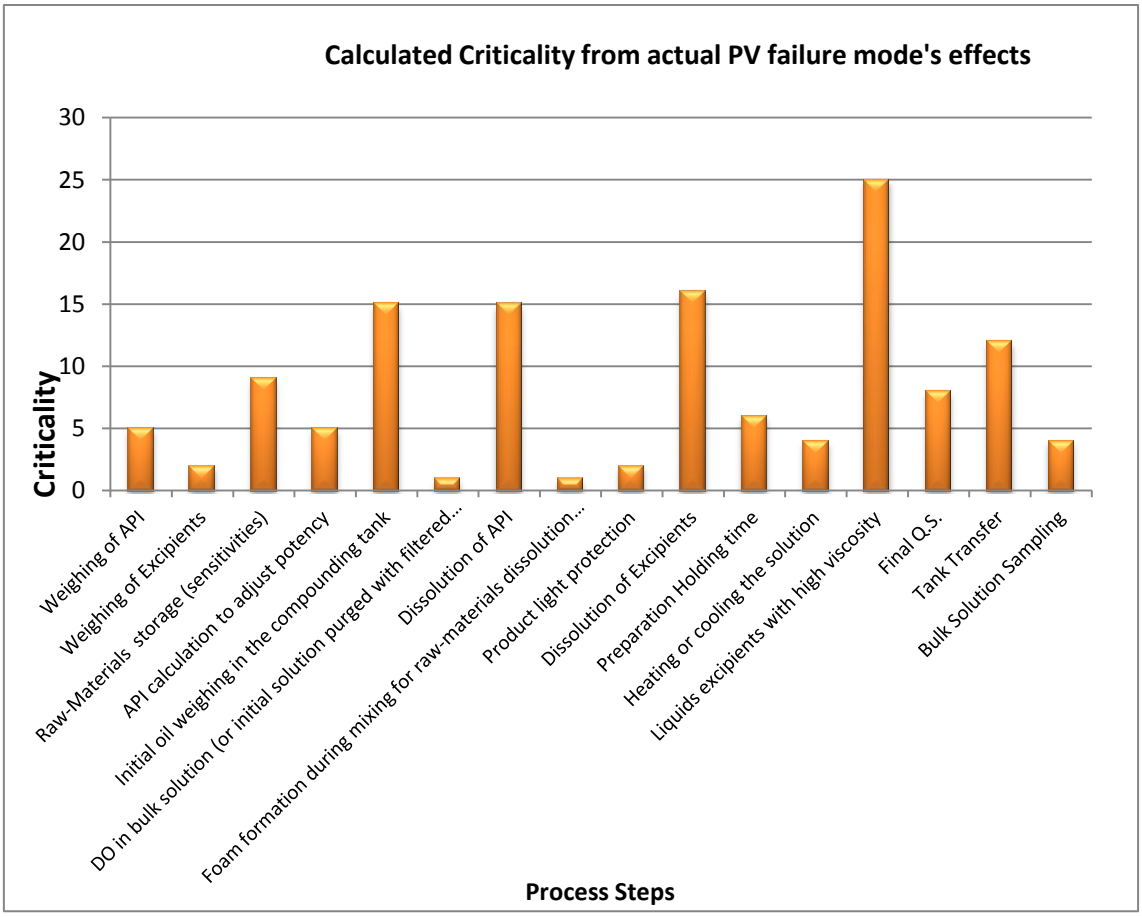


Figure 53: Graph showing the criticality levels for the studied process steps.

According to the calculated criticality the critical obtained procedure is “Transfer liquid RMs with high viscosity” (**Figure 53**). Also RPN were calculated and it was concordantly high (equal to 125) (**Figure 54**). A question was raised: *Can the trend of high assay results be correlated with the incorrect addition of viscous liquids to the tank?* The procedures were evaluated. Since this compounding process (was originally a tech transfer process for a client) it has no need for q.s. and all added raw-materials are previously weighted, it might have a huge impact on final volume/ weight but it had been never verified.

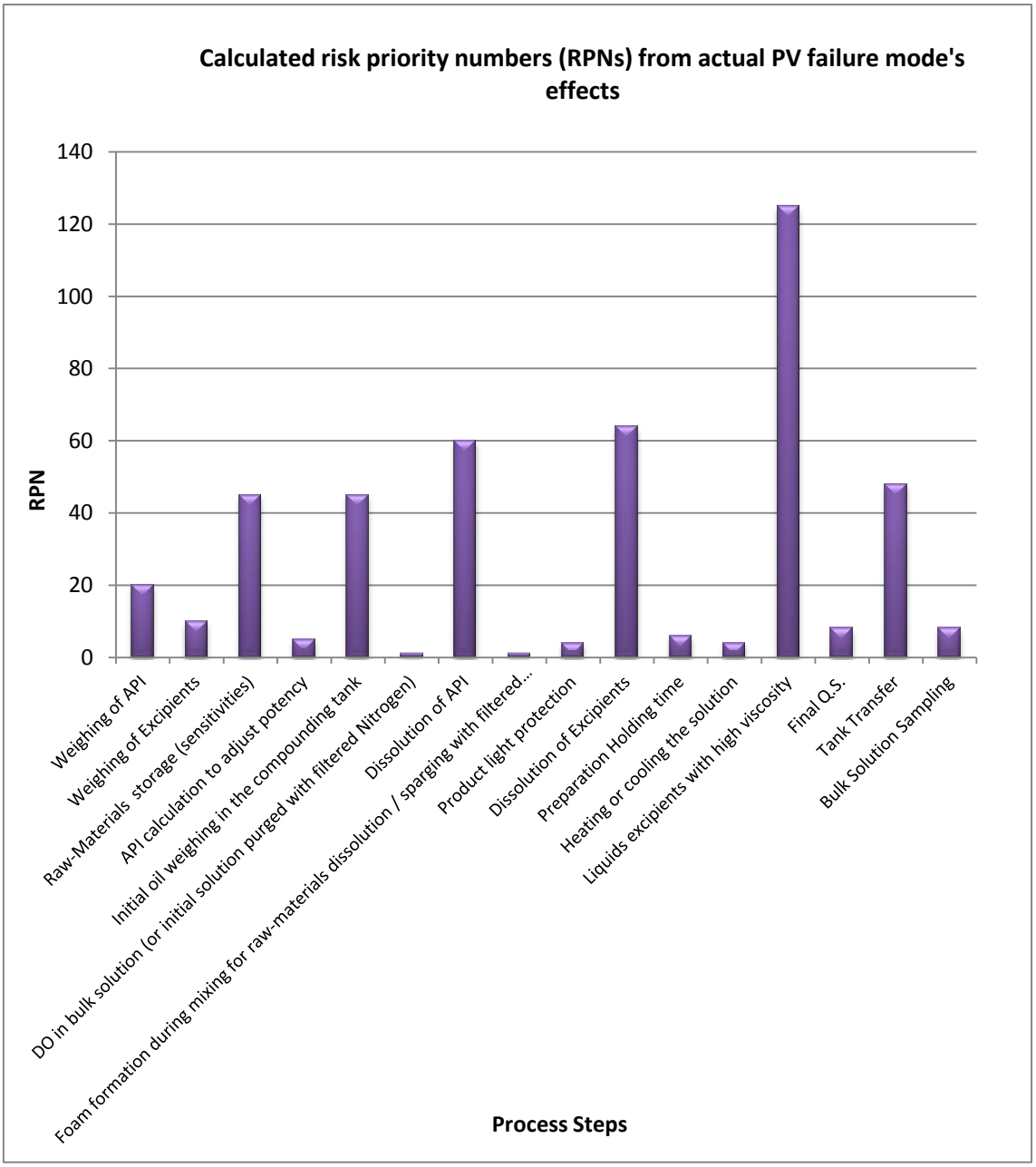


Figure 54: Graph showing the RPN results for the studied process steps.

Three bulk solutions prepared by different operators were supervised. The first component added to the preparation tank is an oil and this initial quantity of oil is directly weight in the tank. The 2nd raw-material added to the preparation tank is a very viscous liquid, previously weight in 4 containers and added directly to the preparation tank. An improper transference of this viscous excipients (oil basis) was performed by all operators. The totality of the this excipient, which was divided into 4 containers, could not be transferred to the preparation tank due to its high viscosity and limitations from maximum compounding time to wait until all oil is poured out from each container into the preparation tank.

Due to the fact that the batch size is only 30 L, it was concluded that the 2 % (in average) more concentrated solution is due to this loss of this viscous excipient. Around 600 mL of oil were not added to the tank and because the final batch was not weigh, this was not noticed.

The following measures were implemented:

- Preparation tank is tared on the floor scale and the weights of every raw-material are double checked.
- In particular, this viscous excipient is weight in the tank in addition to the 1st excipient that was already weighted initially in the tank.
- The final weight is confirmed and the floor scale print out has to be added to the batch record.

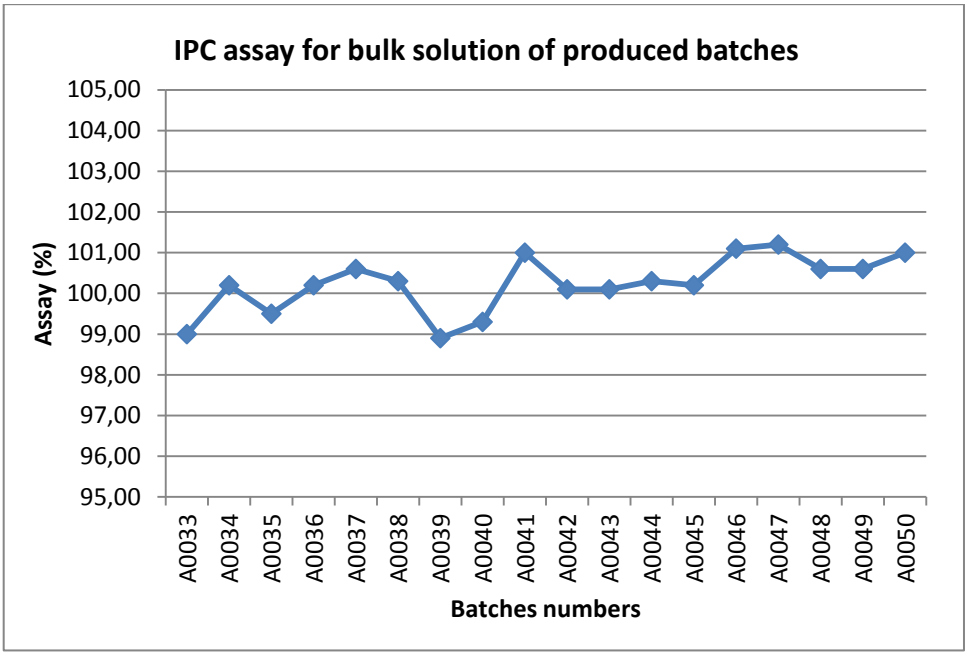


Figure 55: IPC assay for bulk solution of produced batches for an oil basis product – after controls had been implemented to the compounding process.

After all these controls had been implemented, the IPC API assay results obtained from batch monitoring indicates results between 99.9 % e 101.2 % and a RSD of 0.7 % (**Figure 55**).

5.5.3 Lyophilized Products

The main purpose of Lyophilization process is to alleviate the effect of water content on finish product and over product shelf-life and keep its Quality Attributes as liquid bulk but in a stable form (powder) for longer time. Normally lyophilized products are very sensitive to heat

light and oxygen, and accordingly the more stable product form is powder. Therefore this case study will focus on the risk control of the process parameters which may directly or indirectly contribute to the alteration of CQAs of Finish Product.

Additionally to water content, temperature plays a key role along manufacturing process, namely during lyophilisation cycle. Combination of Temperature and Water content influence two critical Product Quality Attributes driving Lyophilization Process Design and Validation:

- Purity
- Solubility

Table 13: Process Parameters that might impact CQAs – Purity and Solubility

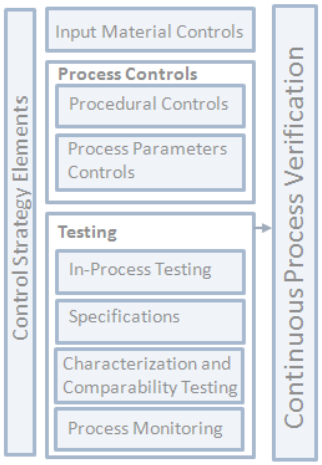
Process Paramaters (influence of water content)	Impact on CQAs	
	Purity of finished product	**Solubility/reconstitution time**
Lyophilisation cycle and water content	Once lyophilisation cycle is initiated as the solution is frozen, any availability of water on liquid form is likely to compromise severely the quality of the product on regards to purity. In extreme situations, if the water content reaches a certain point, melt back phenomena can occur.	The availability of water during the lyophilisation cycle influences structural formation of the crystals which has direct impact on product solubility. This effect can be detected at time zero after lyophilisation or detected during shelf life.
Water content on finished product	Water content of finished product typically affects product purity by promoting degradation over shelf life. The optimal percentage of water content is product dependent, however, for the majority of products the quality/stability increases with the decrease of water content.	Water content of finished product influences severely the solubility of finished product. This effect can be detected at time zero or detected during shelf life.
Temperature during lyophilisation cycle	Affects directly product stability	Influences structural formation of the crystals which has direct impact on product solubility

Although, the temperature and water content seems to be controlled for initial Product Performance Quality during filling and lyophilisation processes, slightly changes might occur with high impact to the CQAs for these very sensitive (lyophilized) products. For these reasons, a continuous process verification and a dynamic control strategy in extremely important lyophilized products. Based on this a design space for CPPs must be carefully studied and challenge.

Table 14: CPPs that impact purity and solubility (CQAs) in Finished Product

Water content – critical in-process attribute	CPPs
Water effect as bulk solution	- Time from compounding until freezing.
Water content during lyophilisation cycle	- Freezing temperature - Primary drying temperature, ramp profile and duration - Condenser capacity vs batch size - Fill volume (influencing cake height) - Secondary drying temperature and duration
Water content of finished product during shelf life	- Water content achieved at time zero - Residual moisture reabsorbed from rubber stoppers

The design space is studied in lab scale and the NOR for each Critical Process Parameter is verified to comply with final specifications set. During a pilot batch the proven acceptable range is challenged in order to confirm that the designed process is suitable for routine commercial manufacturing that can consistently deliver a product within specifications. After that a proposed range for commercial scale is set in order to start production of PPQ batches. For this case study the parameters and controls are described below in **Figure 13**.



Before the production of PPQ batches of an Hikma product “B” extremely sensitive to heat and moisture (water content in finish product increases impurity “H”), the following **Table 15** was design to ensure the correct and needed controls to the process, and showing that the Primary drying step should be determined for each cycle by a pressure rise test.

Table 15: Continuous Process Verification approach for a Lyophilized Product

Factor	PARAMETERS (or ATTRIBUTES)	Range studied (lab scale)	Actual data for the exhibit batch (pilot scale)	Proposed range for commercial scale Θ	Proposed Control (can change during batches comparison and monitoring)
Lyophilization Process **In-Process Controls (TESTING)**					
	Impurity "H" Δ	NMT 0.5 %			
	Water content Δ	0.3 – 1.5 %			
	Reconstitution time Δ	NMT 1 min			
Product Drying (cycle) **Process Parameters Controls**					**Specifications (TESTING)**
Freezing	**Shelf temperature set point**	(-50) – (-55) °C	-55 °C	-55 °C	To ensure all lyo CQAs (assay, water content, reconstitution time, RS content)
	Step duration Δ	6 - 8 hours	7 hours	7 hours	
Primary drying	**Shelf ramp to primary drying**	1 - 3 °C/min	2 °C/min	2 - 3 °C/min	
	Shelf temperature Δ	20 - 30 °C	25 °C	20 - 30 °C	
	Shelf temperature set point	25 °C	25 °C	25 °C	
	Step duration Δ	15 - 19 hours	17 hours	to be determined based on the pressure rise test	
	Chamber pressure	0.001 - 0.01 mbar	0.005 - 0.009 mbar	0.001 - 0.01 mbar	
	Chamber pressure alarm	0.03 mbar	0.03 mbar	0.03 mbar	
Secondary drying	**Shelf temperature** Δ	30 - 40 °C	35 °C	30 - 40 °C	
	Step duration Δ	7 - 9 hours	8 hours	8 hours	
Product Drying (cycle) **In-Process Controls (Product)**					
Primary drying Time		17 hours ± 2 hours			
Product Temperature		20 ± 10 °C			

KEY for DESIGN SPACE VERIFICATION

Δ	Critical input material attributes (CMA), critical process parameters (CPP) or critical quality atributes (CQA) of in-process material or final drug product
Θ	The proposed operating ranges for commercial scale will be qualified and **continually verified**

5.5.4 Suspensions

The last Hikma case study was an injectable suspension "**BetaM**" which had a variable particle sizes even though with specification. Also, the density of in finish product was near the lower limit.

a) Particle size (CQA) variation

The first step was to understand how particle size distribution changed over the last produced batches. The study was started through a detailed analysis of product development where it was clearly specified that the suspension could be unstable above 20 °C. This was an indication that temperature was playing a role on particle sizes variation.

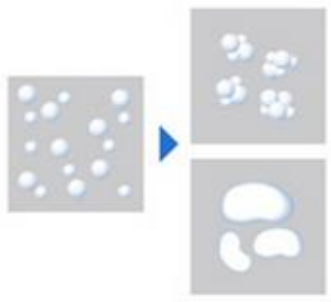


Figure 56: Unstable size change for suspension "**BetaM**"

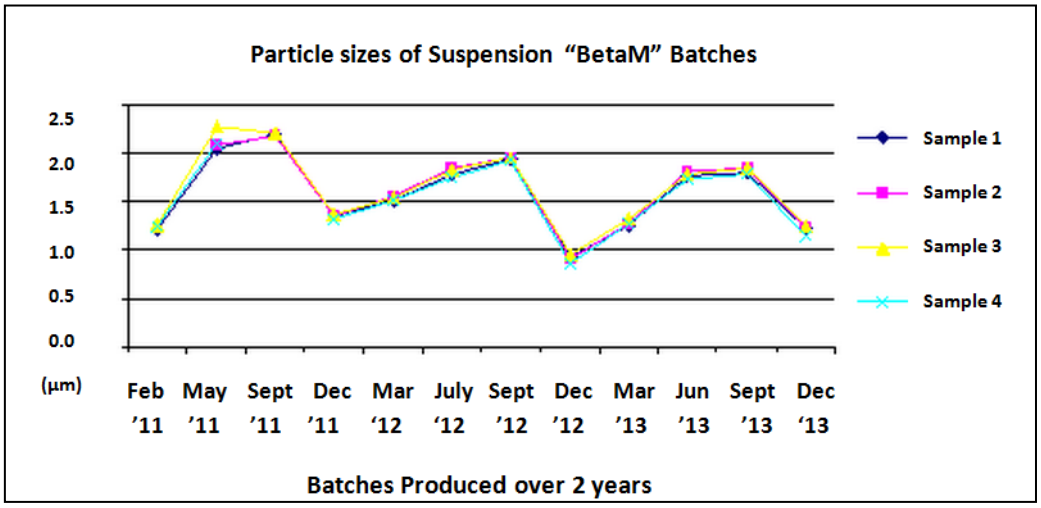


Figure 57: Particle sizes of the last produced Suspensions "BetaM".

Based on the analysis of **Figure 57**, it was concluded that the variation of temperature over the years could influence the differences of particle sizes. Therefore, it was decided to control the filling temperature at 18 ºC. It is expected that the unstable suspension (**Figure 57**) become a stable size suspension (**Figure 58**).

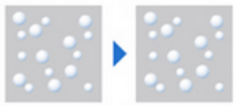


Figure 58: Stable size change for suspension "**BetaM**"

b) Density (CQA) variation

The second step was to understand what could be the causes for density variability. For one of the batches a PHA worksheet was given to the operators to describe possible risks during aseptic filling. This applies for operators' prior experience or knowledge of hazard to identify future hazards, hazardous situation.

Table 16: PHA worksheet for a suspension with low density results

System: *Suspension*			***Operating mode:*** *Aseptic filling*			***Analyst/Date:*** *07.10.2013*	
Product	***Hazard***	***Accidental event*** *(what, where, when)*	***Probable causes***	***Contingencies / Preventive actions***	***Probability***	***Severity***	***Comments***
"BetaM"	Insuficient mixing speed	Not homogeneous solution in the validated mixing speed range	Tank equivalence assumption (differed tank from the one used in initial PPQ batches)	Validated the mixing speed for the product during filling	high	high	PPQ speed (CPP) and density (CQA) have to be performed

A PPQ plan was written and three PPQ batches were compounded and filled in sterile room with the current tank. Samples filled at 3 different speeds (one from each batch) were collected and density was analysed. It was confirmed an insufficient agitation speed before this risk analysis and the new range for mixing speed was implement.

In conclusion, with both CPPs (mixing speed and filling temperature) controlled, the process was considered in state of control.

Chapter 6 GENERAL DISCUSSION

The industry has moved into taking a risk based approach to validation and this makes perfect sense; adopt a proficient risk management methodology, identifying risks and avoiding building uncontrolled manufacturing processes. Along with the new guidelines, the repetition of process qualification and product lifecycle validation phrases illustrates that this is a complete new world from now on. In order to support the new requirements, the suggested Hikma risk approach for process validation promises to minimize process risk and ensure the required confidence prior to distribution of the product.

An important objective of this thesis was the possibility to give Hikma a perspective to implement process validation over product lifecycle. The suggested quality risk management system, based on the latest FDA guidelines, demonstrates that the combination of process parameters and material attributes established at pilot scale during pharmaceutical development are capable of delivering an appropriate quality product on a commercial scale. With the work developed in this thesis it is aimed that the state of manufacturing in Hikma gains an extensive knowledge about critical product and process parameters and quality attributes of its products. Following this line of manufacturing, Hikma strive for continuous improvement.

The scientific and data driven process suggested by Hikma risk approach will reduce subjectivity, quantitative as well as qualitative assessment will assess process risks. This approach will allow risks prioritization and controls risk to an appropriate and acceptable level. The valuable general Risk Assessment for Hikma injectable products created will assess products' risk framework and enable the design of process validation plan based on a scientific- and risk based approach. A risk approach for process validation it does not mean doing less, but doing the right amount at the right time and avoiding non-value added activities as well as missing any crucial validation activity.

The risk-based approach discussed is based in statistical tools, and in a scientific manner elucidate the appropriate methods to evaluate risks and process variability. With continued process monitoring and studying trends over time, Hikma may be able to discover real problems early enough to prevent process failures, product losses, and expensive mistakes.

In order to make more efficient and resourceful the application of risk approach and to facilitate the evaluation of new and existent products at Hikma, statistical and risk tools had been described and studied. The summary of common statistical and risk tools described in this thesis should support the risk approach. However, none of the defining, evaluating, trending, and monitoring described in this thesis and the strategy for design space verification can occur without knowledgeable analytical personnel using dependable equipment to perform robust and reproducible laboratory methods behind manufacturing scenes.

The bottom line is to consider that people see things from different angles – and quite rightly also. The more time spend up front on the risk assessment means that validation effort is reduced and usually more robust to go with it. In this way Hikma relies upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality. By assuring the conformity of all the parameters of the manufacturing process, we may guarantee at the end that the product has the expected quality. Moreover, ongoing process verification optimizes a validated process.

Chapter 7 CONCLUSIONS

In conclusion the way Raw-materials CQA and a variety of parameters are related with Finished Product CQA must be capable of delivering a product of appropriate quality on a commercial scale. This study aimed to present a risk-based approach to evaluate the scope of process validation activities in Hikma. Through the use of the risk tools, an objective assessment of potential uncertainties and their effect on products` critical quality attributes were evaluated and organized to make the most optimal decisions. Furthermore, the described approach risk-based also provided a consistent methodology for decision making which was easily aligned with Hikma goals such as resources allocation and ensuring patient safety and quality products; by building quality into processes and consequently into products. Ultimately, through the consistent use of statistic tools to monitor the variation and maintain processes in state of control along product lifecycle, the number of surprises and their impact will be minimized. The goal of this work was achieved. Assess to products´ risk framework will be provided to production teams during Process Performance qualification and over products lifecycle based in scientific rational by using recognized language, structure and tools.

Certainly, the work described in this thesis has provided additional insights into what is already known about Injectables Manufacturing Process Validation based on Risk Assessment in Hikma Farmcêutica Portugal S.A. and Thymoorgan Pharmazie GmbH. Optimization and improvement of Hikma risk based tools, methods of analyses and procedures will lead the company to higher levels of quality and compliance.

It is becoming increasingly clear that a continuing improving and implementation of this risk management tools is essential to accomplish FDA requirements and to compete at a very high quality level assuring at the same time efficient processes.

Process Validation is a transitioning from a check-box activity to value-added. There is interplay between raw-materials, process parameters, controls, and final outcomes (drug products). A systematic approach that emphasizes product and process understanding and process control, based on scientific operations and quality risk management is the key for innovation and continual improvement.

Concluding, validation is a lifecycle which is living and breathing, it has matured with age and doesn`t have to be cumbersome anymore.

Chapter 8 FUTURE PERSPECTIVES

In a near future design space limits as other process parameters limits can be challenge with computational simulations and a specialized team should be trained in simulators software and be extended to Risk Management system for other Hikma medicines forms – syrups, tablets, sprays solutions, capsules, suspensions, etc.

Moreover, it is almost impossible to achieve the FDA requirements, concerning to ensure uniform collection and assessment of information about the process in product lifecycle, without using a software platform in order to access information quickly throughout the product lifecycle. It is necessary a Validation Lifecycle Management system in order to access, aggregate, analyze, and understand the data generated. With this system, Hikma could provide report data, on demand and in meaningful context, such as a report that allows a combination with PAT approach correlating upstream parameters with downstream process outcomes (automatically accounting for batch genealogy) during both process design and commercial operations.

Within the same system, users should be able to define the risk levels for each of the key factors; severity, likelihood of occurrence, and detectability, in a similar way as it was designed this Hikma risk approach. The system would automatically calculate the risk class and risk priority. Based on the risk, users could effectively build appropriate testing to test the degree of variation to mitigate those risks.

The leveraging data in the right way can enable greater Process Intelligence, which assists with control variability and quality improvements and results in higher yields and accelerates the time to market.

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APPENDIX

Table-A 1: Risk Assessment applied to the oil case study – Process Phases: Weighing and Compounding

Manufacturing Process Parameters and Consequences of Failure										RISK ASSESSMENT / RISK REDUCTION FMECA - Failure Mode Effects and Criticality Analysis			
Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5*** *[1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5*** *[1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5*** *[1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
warehouse/ preparation for compounding	W1	Weighing of API	Incorrect weight.	Low or high assay results (OOS bulk IPC); batch failure.	5	Wrong calibration of the scales. Human error during weighing.	1	IPC assay (fill volume adjustment in order to compensate the difference on potency). Scales are calibrated daily. All weights are triple verified by both compounding operators and QA.	4	5	20	**Low RISK further test to be evaluated**	Comparation of Hikma CoA results with Supplier CoA results in order to confirm the results are aligned.
	W2	Weighing of Excipients	Incorrect weight.	Bulk solution IPC OOS. Finished Product OOS. Reduced stability.	2	Wrong calibration of the scales. Human error during weighing.	1	Scales are calibrated daily. All weights are double verified by both compounding operators and QA.	5	2	10	**No RISK no further test is required**	Controlled conditions to weight hygroscopy raw-materials. Low ventilation to weight light and fluffy powders.
	W3	Raw-Materials storage (sensitivities)	Raw-materials not overlayed with nitrogen; Not protected from light; not stored under appropriate conditions	Raw-materials degradation (high content of impurities) and decrease of potency	3	Human error (storage conditions not followed); If raw materials is not kept in the original container until production day.	3	All Raw-materials are sampled under laminar flow and the top of the containers overlayed with Nitrogen; here are specific instructions in SOPs and batch records	5	9	45	**Med RISK further test required**	Raw-materials included in SOP compiling the conditions for the weighing
	W4	API calculation to adjust potency	Added amount of API is higher or lower than required	Low or high assay results (OOS bulk IPC); batch failure	5	API assay, Water content or Solvents wrongly reported in the CoA used for calculations; Human error in calculations	1	Calculation of API is double verified bedsore weighing and recorded in the MBR. All weights are double verified by both compounding operators and QA.	1	5	5	**No RISK no further test is required**	Formulas for API calculation adjustment revised by Quality Unit Director or QC Manager at the moment of Batch records approval

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Compounding	C1	Initial WFI / oil / liquid excipient weighing in the compounding tank	Incorrect weight.	Low or high assay results (OOS bulk IPC); batch failure.	5	Wrong calibration of the scales. Human error during weighing.	3	Scales are calibrated daily. All weights are double verified by both compounding operators and QA.	3	15	45	**Med RISK further test required**	N/A
	C2	DO in bulk solution (or initial solution purged with filtered Nitrogen)	Oxygen content higher than x mg/ L	API degradation. Preservatives (if present) that reduce the reactive oxygen in solution are consumed immediately. Reduced product stability.	1	Oxygen sensor malfunction. Human errors (high mixing speed allow oxygen in the solution; tank not closed after purging)	1	Control of DO in solution using an oxygen sensor daily calibrated.	1	1	1	**No RISK no further test is required**	Oxygen sensitivity and stability studies for different headspace oxygen percentages.
	C3	Dissolution of API	Insufficient mixing time and/ or speed; or over mixing	Incomplete dissolution of API; Bulk solution does not need IPC specifications	5	Human error; incorrect visual evaluation of dissolution	3	Mixing speed in vortex is evaluated during all PPQ batches in order to validate a range. Samples are taken from the bottom for visual check of API dissolution.	4	15	60	**Med RISK further test required**	Closely monitored during validation studies (time and mixed speed)

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Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5*** *[1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5*** *[1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5*** *[1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	C4	Foam formation during mixing for raw-materials dissolution / sparging with filtered nitrogen	Flow rate of nitrogen sparging is high or mixing speed is high.	Product (foam) comes out from the tank; high DO with no possibility to continue sparging; visual confirmation of raw-materials dissolution is impossible. Bulk IPC OOS,	1	Human error; insufficient monitoring of batch preparation	1	Products forming foam are compounded in bigger tanks size than the set batch size. Nitrogen overlay helps to control the foam.	1	1	1	**No RISK no further test is required**	Prior to PPQ confirm the possibility of bulk solution forms foam; and design the process with an appropriate tank size for compounding accordingly
	C5	Product light protection	tank entrance not closed or covered with aluminium foil between raw-materials addition	API degradation. Reduced product stability.	1	Human error.	2	Operators are trained in product specificities and sensibilities. No other controls are implemented.	2	2	4	**No RISK no further test is required**	Photostability studies.
	C6	Dissolution of Excipients	Insufficient mixing time and/ or speed; or over mixing	Incomplete dissolution of API; Bulk solution does not meed IPC specifications	4	Human error; incorrect visual evaluation of dissolution.	4	Mixing speed in vortex is evaluated during all PPQ batches in order to validate a range. Samples are taken from the bottom.	4	16	64	**Med RISK further test required**	Reference time for mixing of excipients in development report. Industrial mixing times and speeds for specific batch in specific tank detailed in Validation Report.

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Process Phase	ID nr.	**Process Step**	**Potential Variation**	**Effect on Entire System**	**(S) Severity (Level of Risk)**	**Cause of Failure**	**(O) Probability of Occurrence**	**Risk Reduction and Risk Evaluation/Process Controls**	**(D) Probability of Detection**	**Criticality**	**RPN value**	**CONCLUSION**	**Validation/ Verification STUDY to be done**
Manufacturing Process Phase	*Identification of Process Step*	***Phase to which belongs the process step***	***RISK***	***Probable consequences / OUTPUTS Failures***	***From 1 to 5*** *[1=low; 5 high]*	***Incorrect INPUTS***	***From 1 to 5*** *[1=rare; 5 frequent]*	*Variability Control*	***From 1 to 5*** *[1=high; 5 low]*	*S x O*	*SxOxD*	***Step Risk***	*Additional Controls / Tests to be implemented during Process Validation*
	C7	Preparation Holding time	Excessive hold time from the API addition to the end of compounding / beginning of lyophilisation cycle OR if volatile excipients in formulation (e.g. ethanol) long holding times for preparation will reduce their content in solution	Increase of impurities	3	Product is not stable for long time in liquid state. Human error, mechanical problem in the line can lead to exceeding the bulk holding time.	2	All critical times have to be studied and documented in the batch record. Solution is stored in sealed tank.	1	6	6	**No RISK no further test is required**	Maximum holding time between API addition and beginning of freezing phase to be evaluated for lyophilized products
	C8	Heating or cooling the solution	Temperature above or below the set limits	Increase of impurities. Dissolution difficulties	4	Human error, mechanical problem (in chiller or heater)	1	Temperature limits for applicable steps are written in the batch records and are double check by 2 compouding operators.	1	4	4	No RISK no further test is required	Or for liquid products - Maximum holding time between API addition and end of filling.
	C10	Liquids excipients with high viscosity	Not totally transferred to preparation tank	Low or high assay (compromise the batch)	5	Human error	5	If these liquids are not weight directly in the preparation tank, there are other actions as mechanical removal with WFI or container wash with bulk solution from the compounding tank (if not removed with another organic solution)	5	25	125	**High RISK further tests and controls required**	Weighing procedures adjusted to different materials viscosities in order to reduce losses

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	C11	Final Q.S.	Human error; balance malfunction	Low or high assay (compromise the batch)	4	Human error, scale malfunction	2	Balance is calibrated and verified prior to each compounding as per SOP. The Q.S. is double verified.	1	8	8	**No RISK no further test is required**	Quantify the water amount to be added to the final Q.S.
	C12	Tank Transfer	Product losses; Contamination; materials incompabilities	Bioburden OOS; High RS content	3	Human error.	4	All tanks are cleaned and sterilized using validated procedures. The compatible materials with product are described in the batch record. The tank holding time after CIP/SIP is qualified. The product holding time in the transference tank is validated for a certain time (can be up to 72 h).	4	12	48	**Med RISK further test required**	Validation study for product transference. Bulk holding time in transference tank.
	C13	Bulk Solution Sampling	Incompatibility with containers; Contamination; use of non-dedicated or disposable materials; incorrect sampling procedures; product oxidation	High results for related substances and low assay results; high bioburden; products cross contamination ; assay OOS. Results not representative of bulk solution (false results). Batch failure.	2	Incorrect sampling procedures. Wrong sampling containers used. High headspace oxygen inside the sampling container that can react with the product.	2	Surfaces compatibility studies are made for Hikma products and requested for clients' products; Operators are trained in compounding GMPs every year; for oxygen sensitive products the sampling container has to be totally filled l no avoid headspace.	2	4	8	**No RISK no further test is required**	Batch sampled in different containers for compatibility surfaces studies.