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A Validation Master Plan for Small Volume Parenterals

Dissertação de Mestrado em Tecnologias do Medicamento, orientada pelo Professor Doutor Francisco Veiga e apresentada à Faculdade de Farmácia da Universidade de Coimbra

Agosto de 2014

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Universidade de Coimbra

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Aknowledgements

To my Family for inspiring me to become a better person and professional.
To Diogo for all the patience and the encouragement.

I would also like to thank everyone that made a special contribution to this dissertation:
Professor Dr. Francisco Veiga for his valuable guidance and supervision.
Fresenius Kabi – Labesfal for giving me this chance to develop my knowledge and experience.
All my colleagues at Fresenius Kabi – Labesfal that shared their knowledge and enriched mine,
especially Unit 2 Small Volume Parenterals Manager, Manuel Vicente.

Index

Abbreviations and Definitions

- API – Active Pharmaceutical Ingredient
- CIP/SIP (Clean-in-Place/Sterilization-in-Place)
- Critical process parameter (CPP)
- Critical quality attribute (CQA)
- Critical Material Attributes (CMAs)
- Design space verification (DSV)
- DOE - Design of Experiments
- DPMO – defects per million opportunities
- DS – Design Space
- EU – European Union
- EP – European Pharmacopoea
- GMP – Good Manufacturing Practices
- ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- LAF – Laminar Air Flow
- LCL – Lower Control Limit
- LSL – Lower Specification Limit
- MIR (Mid Infrared)
- Multivariate Statistical Process Control (MSPC)
- NIR (Near Infrared Sprectroscopy)
- NMT – Not more Than
- Normal Operating Range (NOR)
- Partial Least Squares (PLS) Regression
- proven acceptable range (PAR)
- PAT – Process Analytical Technology
- PCI (process capability index)
- PPQ - Process performance qualification
- Principal Component Regression (PCR)
- QTPP - Quality Target Product Profile
- SOP – Standard Operating Procedure
- SPC – Statistical Process Control

- UCL – Upper Control Limit
- USL – Upper Specification Limit

Abstract

With the launch of the Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach Guideline as well as the ICH Q8, Q9 and Q10 guidelines, the paradigm regarding quality started to change. This resulted in the launch of a Process Validation Guideline by FDA in 2011. This Guideline changed the perception of the Process Validation from an initial fixed procedure, to a lifecycle approach.

Therefore, Process Validation is now understood as a way to understand the sources for variation and how it should be managed. Before, the processes were fixed and the variable inputs resulted in variable outputs. Now, if the inputs are known, the process can be adjusted so that the output is consistent. The higher the knowledge of the variation and the process, the better the variation is controlled and the lower is the process risk.

.Following FDA, EMA launched in 2014 a new revision for the Guideline on the Process Validation for Regulatory Submissions. This Guideline was the first European Regulation to address Process validation as a lifecycle approach. This lead also to the revision of Annex 15 of the European GMPs, being the draft under consultation.

The objective of this project is to identify the essential CQAs and CPPs for the manufacturing of ampoules in order to establish a Master Plan for all the products manufactures in the Small Volume Parenterals Line. Also, Continuous Process Verification was applied to one product to analyse the capability of the process to manufacture a quality product.

1. Introduction

Quality can be defined in several ways. According to ICH guidelines, quality is defined as the suitability of the drug substance or drug product for its intended use.[1] It can also be defined as a question of reliability or conformance to standards. The traditional way of defining quality is based on the viewpoint that products and services must meet the requirements of those who use them.

Generally, there are two aspects of suitability for use: quality of design and quality of conformance. Quality of design is associated with the levels of quality created in to the product, thus being intentional. Quality of conformance is associated to the compliance with the specifications required by the design. This can be influenced by a number of factors, including the choice of manufacturing processes, the training and supervising of the operators, the types of process controls and tests that are employed and the extent to which these procedures are followed.

Regarding medicines, from the patient point of view, Quality should mean safety and efficacy, as well as availability when needed. Moreover, patients rely that the drug is correctly identified, delivers the same performance as descripted on the label throughout the shelf life and is produced in a way that ensures quality.

Good Manufacturing Practices for Medicines have been developed in the 1960s, having introduced the concept of process validation at the time. The first most detailed description was published in 1987 with the FDA's Guideline on General Principles of Process Validation. Since then many other guidelines emerged.[2]

However, since 1987 the concept has changed. It passed from "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting it predetermined specifications and quality attributes"[3], to "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" in the 2011 guideline. [4] This Paradigm shift was initiated in the Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach Guideline as well as the ICH Q8, Q9 and Q10 guidelines and will be explained in this document.[1]

2. Manufacturing Process Validation - New Concept

According to EU GMP Chapter 5, all critical processes should be validated.[5] Manufacturing Process Validation is defined as the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes according to Annex 15 of the EU GMPs.[6] Therefore, Manufacturing Process Validation is performed in order to demonstrate that the process is reproducible and consistent. Formerly, in order to demonstrate this, three runs of the process were performed. These three batches, that being compliant with the specifications, meant that the process was reproducible and could be performed routinely. In such cases, the validation effort ended when the product was successfully launched and through the lifecycle of the product there were little or no further considerations on validation.[2]

In September 2003 there was a paper in the Wall Street Journal – "New Prescription for Drug Makers" - that showed that the Pharmaceutical Industry Process was about to change. This paper stated that it seemed more important to manufacture drugs precisely to specification, using tried-and-true systems, than to latch on to the latest in manufacturing trends. This paper also states that FDA has concluded that the industry needs to adopt manufacturing innovations, partly to raise quality standards. [7] In August 2002, the FDA had announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality, starting the mind-set shift. PAT (Process Analytical Technology) Guidance for Industry was also released in September 2004, which contributed to the encouragement of the development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. [8,9,10,11]

With the release of the FDA's Guidance for Industry in 2011, the concept for the Validation started to change. 1987 FDA Guideline defined the process validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics". The new Guideline revision integrates the concepts of ICH Guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System), implementing the Validation activity during the product lifecycle. This guideline defines the process validation as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Although there are no drastic

differences between the two definitions, it is in the application of the concepts that there is the strongest difference. Process Validation is now looked as an ongoing program instead of being an on-off event.[8]

The implementation of this new approach through the product Lifecycle began with the implementation of Q8, Q9 and Q10, as well as the PAT Guidance. These guidelines provide a Science and risk-based approach enhancing the quality of the product, which is applicable throughout the product lifecycle. The structured way to define product Critical Quality Attributes (CQA), design space, the manufacturing process and the Control Strategy of these parameters are introduced by these guidelines.[8]

EMA published a Guideline on Process Validation for finished products in February 2014 incorporating the above mentioned concepts into the process validation and indicating the data to be provided in regulatory submission. Annex 15 of the EU-GMP Guide is also in revision following the publication of the guideline, according to the concept paper released in November 2012, establishing the connection between the new Guideline and the GMP requirements of the manufacturing industry.[12,13,14]

Process Validation is now understood as a way to understand the sources for variation and how to manage it. Before, the processes were fixed and the variable inputs resulted in variable outputs. Now, if the inputs are known, the process can be adjusted so that the output is consistent. The higher the knowledge of the variation and the process, the better the variation is controlled and the lower is the process risk.[8]

All the changes in the regulations had to a new definition and mindset regarding manufacturing process validation and processing.

2.1. FDA Guideline

The 2011 FDA Guideline defines Process Validation 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". This is established through three stages: Process Design, Process Qualification and Continued Process Verification. [4]

Process Design should be performed during Development stage, while Process Qualification should be performed before selling the product. The last stage, Continued Process Verification, should be performed during Commercialization. [8]

This concept enhances the connection between the development and the manufacturing, as all the knowledge gained during manufacturing will be integrated in the manufacturing, helping to understand the product and the process.[8]

In order to be a success, the validation process depends upon the information from product and process development that should enable the knowledge of the variations through the process. Manufacturers should understand the sources of variation, detect the presence and measure the degree of variation, understand its impact on the process and on the product attributes, as well as manage it in order to commensurate with the risk it represent to the process and product. It is understood that the better the process is understood, the better the variation is eliminated. Process Validation is thus an on-going process during the product lifecycle.[10]

2.1.1. Stage 1 – Process Design

This stage involves the definition of the manufacturing process that will be implemented in the routine production activities for commercial batches. During this stage the knowledge and understanding of the process should be built, so that the commercial production and control steps are defined. The decisions and justifications of the controls should be documented in order to use them in the commercial batches production, as well as in the Continued Process Verification procedure. The production operations should be verified in all operating ranges and the variables for an operation should be identified as significant.[4,15]

In this stage, Design of Experiments (DOE) can be used to identify and reveal relationships between process parameters or component characteristics and the resulting outputs, in accordance to Risk analysis tools, providing data to investigate the source of variability. Risk management efforts should ensure at this phase that the product process knowledge is attained so that the development efforts can be prioritized and ranked according to the CQAs.[4]

After this first step, there must be documented strategies for process control in order to reduce input variation, adjusting the process according to this variation (so that reduces the impact on the output) or to combine both strategies. These strategies should be defined according to a risk analysis, with the definition of the type and extent of process controls, aided by the process experience, in order to minimize and prioritize the effort. The goal is to control the process so that the output is consistent, adjusting it to the variables of the inputs.[4]

2.1.2. Stage 2 – Process Qualification

During this stage the process design is confirmed as being capable of reproducible commercial manufacturing. This is the stage before the commercialization of the product where it is verified if the product can start to be commercialized. This stage comprises two steps:

1. Design of the facility and qualification of the equipment and utilities;
2. Process performance qualification (PPQ).[4]

Step one includes the selection of the facilities, utilities and equipments and its verification according to GMPs and according to the specific use, but the guideline does not refer common used terns as IQ or OQ that are commonly used in this phase. The guideline states that Verification should be performed to demonstrate the fitness for intended use. Verification, according to ASTM E2500 is defined as a systematic approach to verify that the manufacturing systems, acting singly or in combination are fit for intended use, have been properly installed, and are operating correctly, being an umbrella term to assure that systems are fit for use such as qualification, commissioning and qualification, verification, system validation or other.[4,8,15]

Verification Process should be performed in the following steps:

- List of all critical aspects (CQA,CCP);
- Elaborate a verification plan;
- Verification testing (Design to performance) to conform Critical Aspects and meet Acceptance Criteria which includes SAT and FAT, but also a Performance testing;
- Acceptance and release for Operation.[8]

Step two combines the facilities, utilities, equipment with the materials and trained personnel in order to produce commercial batches and verify if the process performs according to the designed expectations, so that the produced medicine is consistently delivered with a high level of quality. PPQ must be successfully performed before the commercialization of the batches, so that it is a significant milestone in the product lifecycle.[4]

PPQ uses the experience obtained during the design of the product, together with the experience attained with similar products. During this process performance qualification, there should be a higher level of sampling, as well as additional testing so that the process is deeper analyzed and the level of scrutiny is higher than in routine monitoring so that the process is clearly characterized.[4]

Process Analytical Technology (PAT) may enable another PPQ approach, as the PAT allows the process to adjust itself in a timely control loop. In this way, PPQ should be more focused in the measurement system and control loop for the measured attribute.[4,11]

PPQ protocol must specify the manufacturing conditions, the data that should be collected and how will it be evaluated, as well as the tests to be performed and the sampling plan. The statistical methods used for analysing and collecting the data and the provision for addressing deviations should also be encompassed in the PPQ Protocol. The data collected from the manufacturing should not be excluded from the PPQ without a documented science-based justification. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.[4]

The report assessing the accomplishment of the PPQ protocol should summarize the data collected and discuss all the aspects of the manufacturing including deviations. This report should also clearly refer if the data collected complies with the stated on the protocol, as well as if the process is controlled. [4]

2.1.3. Stage 3 – Continued Process Verification

During this step there should be a continuous evaluation of the process, as it should remain under control during commercial manufacturing. This stage is more than a Product Quality review, as this stage involves the use of a system or various systems of assuring control. There should be a system to collect and analyse the product and process data that relate to product quality. This data should show that the quality attributes are being properly controlled during the process, as well as the process stability and capability. This monitoring should be performed at the level established during PQ until significant data is available to generate significant variability estimates.[4]

Continued Process Verification's key systems are the process performance and product quality monitoring system tools, which consist on the definition of a

control strategy that can include the monitoring of the parameters and attributes related with the drug substance within the defined equipment operating conditions and in process controls.[8]

A summary of the points mentioned in the guideline is given below: [16]

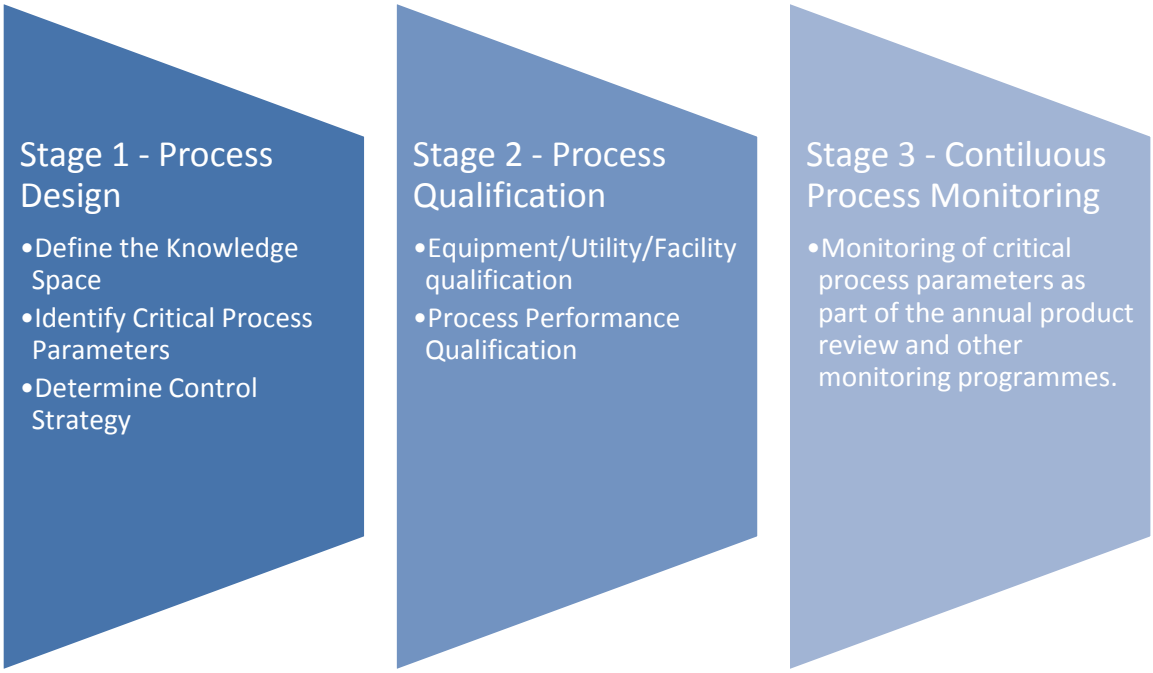


Figure 1 . – Process Validation Stages

2.2. EMA Guideline on Process Validation

EMA published the new Guideline on 27th February 2014, after publishing a draft version on March 2012. Considering the previous revision, the title was changed to "Guideline on process validation for finished products - information and data to be provided in regulatory submissions", which states clearly that the document concerns only regulatory data to be submitted and has not the aim to be a GMP document. So, this should be in line with Annex 15 of the EU GMPs, so that they will impact on each other.[12,13]

According to this guideline, the purpose of Process Validation remains that a designed manufacturing process yields a product meeting its predefined quality criteria. ICH Q8, Q9 and Q10 provide a structured way to define product CQAs, Design Space the Manufacturing Process and the Control Strategy.[12,17]

Process validation should be built in a lifecycle approach that binds the product and process development, together with the validation of commercial manufacturing process as well as the maintenance of the process in a state of control during routine commercial production. Process design, Process Validation and On-going Process Verification can be considered as stages of the Product Lifecycle.[12]

According to current version of Annex 15 of the GMPs, the manufacturing Process should be validated before the product is placed on the market, although, in exceptional cases, concurrent validation may be accepted. Process validation should cover all product strengths and batch sizes, manufactured in all manufacturing sites, so that it demonstrates that the processes are suitable for manufacturing a quality product at each site of manufacture.[13]

Process validation can be performed according to different approaches: Traditional Process Validation, Continuous Process Verification and Hybrid Approach.[12]

2.2.1. Traditional Process Validation

This approach refers to the traditional way of validation, where the validation batches are manufactured and approved leading to the commercial routine production. The process validation should be performed when the process development is concluded, demonstrating that the process is suitable for the manufacture of the product in each manufacturing site. This validation studies may be conducted in pilot scale batches if the process is not yet transposed to commercial scale. The batches should be in minimum 3, depending on the variability and complexity of the process and the product and the experience of the manufacturer.[12,17,18]

2.2.2. Continuous Process Verification

Continuous Process Verification is described as an additional step or an alternative to the Traditional Process Validation, implementing the concepts from ICH Q8, so that the process performance is continuously monitored and evaluated.[12,17,18]

This Verification is based on continuous monitoring of the processes, assuring that is complies with the CQAs and CPPs, operating within the predefined specified parameters. PAT should have a key role at the conception, analysis and control of the processes based on "on-line", "at-line" and "in-line"

measurements of the CQAs in process, in order to assure the product quality. These measurements can be defined as:

- "on-line" –measurement where the sample is removed from the process and can be returned after the measurement;
- "at-line" – measurement where the sample is removed, isolated and analysed near the process flow;
- "in-line" – invasive measurement where the sample is not removed from the manufacturing process.[11]

Continuous Process Verification can also be reinforced by Multivariate Statistical Process Control (MSPC), which together with PAT can help to gain process knowledge and assure that it complies with the proposed CPPs and that it delivers a quality product that complies with the proposed CQAs.

Continuous Process Verification can be influenced by:

- Prior knowledge of similar products and processes;
- The experience and process understanding gained during development phase;
- The complexity of the process and the product to be manufactured;
- The analytical processes used and process automation;
- The process robustness and manufacturing history.[12,17,18]

Continuous Process Verification can be introduced in any point during the product lifecycle: it can be used to during the initial production to design process validation protocols, during revalidation of already commercialized products or supporting continuous improvement during the product lifecycle.[12,17,18]

2.2.3. Hybrid Approach

This approach can be useful when it is necessary to use either the traditional process validation or Continuous Process Verification in different steps of manufacturing, if clearly defined and justified in the dossier.[12,17,18]

2.2.4. Design Space Verification

During scale up processes, the process is generally conducted and validated in a specific area of the Design space, referred as the Normal Operating Range (NOR). Thus, during product lifecycle, depending on the initial establishment of the design space, it might be necessary to confirm the suitability of the design space and verify that the product meets all CQAs in the new area of operation within the design space. Depending on how the design space was originally established and how the process was validated, there will be situations where it will be necessary to confirm the suitability of the design space and to verify that all product quality attributes are still being met in the new area of operation within the design space.[12,17,18]

If during the development of the design space, the parameters used to investigate are shown to be scale dependent, there might be two approaches to the Design Space verification (DSV). If the initial validation was used with traditional process validation, the DSV is required with a verification protocol. Depending on the change and the extent of movement in the design space, the protocols for DSV should include CQAs and CPPs not included in the routine system verification. It is not necessary to verify entire areas of the Design Space or the limits of the process ("edge of failure"). A stepwise approach taking into consideration the need to adjust the NOR within the approved design space during product lifecycle is acceptable. If Continuous Process Verification is used, this may demonstrate that the process remains in a state of control within the design space. So in this last case, as DSV strategy should be included in the Continuous Process Verification.[12,17,18,19]

2.3. Annex 15 Draft

In February 2014, after the launch of the new EMA Guideline, the EU Commission issued the new draft of the Annex 15 "Qualification and Validation" to the EU GMP Guide. The reason for the draft is stated on the Concept Paper on the revision of Annex 15, being adjustments regarding:

- Changes in Part I of the EU GMP Guide;
- Changes in Annex 11;
- ICH documents Q8/Q9/Q10 and Q11;
- The EMA Guideline on Process Validation;
- Changes in manufacturing technologies.[13,14]

New points have been added to the table of contents like subparts of the Process Validation Chapter, topics on transport verification, packaging validation, qualification of utilities, and validation of test methods. The issue revalidation has been replaced by requalification.

In the chapter "Principle", the new draft emphasises the need to assess the impact on the validated status or control strategy of the changes to the facilities, equipment, utilities and processes.[13,14]

There is a new section ("General") in which a justified and documented risk analysis (as part of the quality risk management approach) should be the basis for decision making regarding the scope and depth of the qualification and validation activities. Also, it refers that the principles of ICH Q8-11 (or others if comparable or better) are mentioned as support for qualification/ validation activities.[13,14,20,21]

The first chapter "Organising and Planning for Qualification and Validation" refers that the process validation activities should be encompassed during the product lifecycle, including in this part the new concept for the validation.[13,14,20,21]

Regarding Process Validation, new Chapter 4 "Process Validation" refers that it should be taken into account together with new EMA Guideline on Process Validation, although it states that the guideline refers to the regulatory requirements and GMPs should extend beyond it. In the draft revision of Annex 15 the definition of process validation has not changed. It is still defined as the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.[13,14,20,21]

Retrospective validation approach is no longer stated in the Annex, instead, it states that a lifecycle approach should be applied linking product and process development, validation of

the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.[13,14,20,21]

This Annex, as also is referred in the EMA Guideline, introduces two approaches for validation: the traditional approach and the continuous verification, stating that irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Process validation should be performed prospectively prior to the commercialization, whenever possible.[13,14,20,21]

Concurrent validation is allowed in a justified and documented risk analysis only if there is a strong risk-benefit to the patient. This approach must be documented in the validation master plan and be approved by authorised personnel. There should be sufficient data to support the conclusion that the process is uniform and can meet the defined acceptance criteria. The results and conclusions should be documented and the conclusion should be available to the Qualified Person prior to the release of the batch.[13,14,20,21]

In the traditional approach, a number of batches of the finished product should be manufactured under routine conditions to confirm reproducibility. The number of batches should be determined by the manufacturer in order to demonstrate that the process is capable of consistently delivering quality product. This definition should be based on quality risk management principles, allowing the normal range of variation and trends to be established. The annex also refers that it is generally considered acceptable a minimum of 3 consecutive batches although an alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. This initial validation should be complemented with further data obtained from subsequent batches as a part of the on-going process verification scheme.[13,14,20,21]

The process validation Protocol should define the CQAs and CPPs and summarise them together with the inclusion of the associated acceptance criteria. The protocol should also contain a summary of non-critical attributes and parameters which will be investigated during the validation activity, being this decision justified. The method validation of the relevant analyses should be stated as well as the criteria for the process for release, if applicable. There should be a rationale for the sampling plan. And furthermore, reasons should be given for the selected in-process controls.[13,14,20,21]

Alternatively to the Traditional approach, Continuous process verification approach should be applied in products developed by a QbD approach, where an established routine process control has been demonstrated to provide a high degree of assurance pf product quality. The Process Verification system should be defined and there should be a science based

approach to define a control strategy for the required CQAs and CPPs. This process can use PAT and Multivariate Statistical Process Control (SPC) as tools, which should be determined by the manufacturer according to the process to be analysed. The number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product should be defined by the manufacturer.[13,14,20,21]

A hybrid approach using the traditional approach and continuous process verification can also be used for different production steps. Where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data, continuous verification may also be used after changes or during ongoing process verification. This applies even if the product was initially validated using a traditional approach.[13,14,20,21]

In the Ongoing Process Verification during Lifecycle, the annex defines that the product quality should be monitored in order to ensure that a state of control is maintained during the product lifecycle. The extent and frequency of this step should be reviewed periodically considering the process understanding and performance during the product lifecycle. This step should be performed under an approved protocol and the results documented in a report. Statistical tools should be used to support any conclusions with regard to variability and capability of a given process so that a state of control is assured.[13,14,20,21]

In this draft, the concept of verification of transportation, validation of packaging, qualification of utilities and validation of test methods are introduced. The concept of revalidation is removed, being the Re-Qualification introduced in chapter 10. Cleaning Validation chapter also suffers a modification by the influence of Q8/Q9 and Q10.[13,14,20,21]

2.4. Comparison between EU and FDA concepts

When the FDA Guideline was published in 2011, it changed the concept of validation. Comparing the FDA Guideline with the EMA Guideline and the Annex 15 draft, it becomes clear that EMA is not looking for creating a guideline to be analogue to the FDA. Although there are some similarities, there are some areas at the FDA document that are not comprised in the EMA documents, and also there are some differences between the two approaches.[19]

The similarities are:

- Incorporation on the validation scheme through the product lifecycle, introduction of quality risk management and quality practices according to ICH Q8, Q9 and Q10;

- Recognition of the importance and benefits of emergent technologies like PAT to support the validation effort;
- Refined detail about the regulatory expectations for adequate validation effort.[19]

The two approaches differ on:

- Number of minimum batches necessary for successful validation prior to commercialization. EMA Guideline and Annex 15 draft refer to a minimum of three consecutive batches, with exceptions to be justified. FDA Guideline affirms that the number of batches should be sufficient to provide statistical confidence at the process.
- FDA Guideline emphasis at the documentation of development phase as a step through the validation. EMA Guideline and Annex 15 draft encourages the development activities but is less descriptive on the requisites.
- EMA admits the application of Continuous Process Verification replacing the traditional validation methodology. FDA Guideline has not much emphasis on the Continuous Process Verification, requiring the three phases of validation to be completed, independently of the methodology used.[19]

FDA Guideline enhances also the Continued Process Verification approach which is the on-going monitoring of the validated state of a process, usually through tools such as statistical analysis of batch data, non-conformances, customer complaints and similar products quality feedback mechanisms. It is a cumulative process across multiple batches, similar to EMA's Ongoing Process Verification. EMA also refers to Continuous Process Verification which is the assessment of a manufacturing process during a batch using on-line, in-line or at-line verification methods.[19]

Both approaches have the same principle: the lifecycle approach to validation. Whichever the approach chosen, there should be a risk assessment conducted prior to initial commercial validation batches, so that it can highlight the areas where particular focus and data is needed to demonstrate the desired consistency of the process. Continuous Process Verification demonstrates the actual level of assurance of process, providing the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be applied throughout the product lifecycle to maintain the process controlled. So, the validation is an ongoing process until product discontinuation.[10]

2.5. Quality by design and Process Optimization

As seen before, the concept of building quality into the product enhances the understanding of the sources of variation along the supply chain in the manufacturing process, detects the existence and grade of variation that is passed to the product and its impact on the product quality as well as how to control these variations.

ICH Q8 Pharmaceutical development addresses the key concepts of QbD and Design Space (DS), as well as establishes the principle of designing quality into products and processes rather than testing for the quality in the final product in the end of the process. This guideline defines DS as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide the assurance of quality. Working within the DS is not considered as a change, as the process can be adjusted within this DS to make continuous improvements without formal regulatory approval.[9]

ICH Q9 Quality risk Management describes a systematic process for the assessment, control, communication and review of quality risks, as well as the tools to identify and manage these risks. These principles and tools can be applied to all aspects of pharmaceutical quality through the product lifecycle including development, manufacturing and distribution.[10]

ICH Q10 Pharmaceutical Quality System outlines the goals of a quality system that can be applied to all phases of a product's lifecycle.[11]

QbD is a scientific, risk-based and proactive approach to pharmaceutical development, which considers the design effort from product conception through commercialization with Full understanding of how product attributes and process relate to product performance.

QbD lowers the costs of quality, as focus the control efforts on the factors that are critical to quality helping a better allocation of resources and improving manufacturing performance. It enhances scientific foundation for review and provides for better coordination across review, compliance and inspection, providing better consistency for the process.

Development of Pharmaceutical products should primarily define the Quality Target Product Profile (QTPP) that is related with the quality, safety and efficacy of the product. This first step should begin with the consideration of the route of administration, dosage form, as well as the other parts of the product profile. Then there should be the identification of the CQA of the product so that these attributes that may have impact on the product quality can be studied and controlled. The determination of the CQAs of the drug substance, as well as of the excipients should be performed too, so that the product attains the desired quality. The manufacturing process should be selected, as well as a control strategy for the CQAs. This system should be enhanced with the QbD, meaning that there should be a systematic

evaluation of the manufacturing process, identifying the material attributes and CPPs that may have effect on the product CQAs, determining as well its relationship and using Risk Management to establish the control strategy.[9]

CPPs are defined as process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. CQAs are defined as a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. A CQA is a physical, chemical, biological, or microbiological property or characteristic, normally associated with the drug substance, excipients or drug product, which should be within an appropriate limit, range, or distribution to ensure the desired product quality.[9]

The relationship between CQAs and CPPs can be described in the design space. This can help to understand the linkage and effect of CPPs and CQAs, and also help identify the variables and their ranges within which consistent quality can be achieved. CPPs and CQAs should be fully described while selected, with their application and impact on product quality. The design space can be detailed within CPPs and CQAs or through more complex mathematical relationships. The design space can be described as a time dependent function or through a combination of variables, so that the product manufactured meets the defined quality. Only the combination of proven acceptable ranges does not constitute a design space. Despite that, these ranges can be useful to the knowledge of the process, as well as to the development of the product. The approach should identify the sources of variability and improve process and product understanding.[9]

2.6. Tools for Continuous Process Verification

2.6.1. Process Analytical Technology

PAT can be defined as a system to collect, analyse and control the production proceed through frequent in process measurements of CQAs or CPPs related to raw materials, intermediate products or processes in order to assure that the finished product meets the quality standards defined.[11]

Conventional pharmaceutical manufacturing is generally performed using batch processing in off-line laboratories that take generally more time and are less efficient. These tests are performed in samples collected at determined time points during production in order to evaluate the product quality. Production

processes are generally not fully understood and thus considered as "black boxes". In this process, the relevant information is limited and obtained after the process, thus making the control more difficult and that can lead to batch rejection.[22]

With PAT scientific knowledge of the manufacturing processes can be justified (leaving the "Black box" concept), meaning, that quality should be built from the beginning and not just tested in the end. PAT should have a crucial role in the conception, analysis and control of the manufacturing process, with "on-line", "at-line" and "in-line" CQAs and CPPs.[22]

The essence of PAT involves the comprehension of the process combined with the CPPs and CQAs monitoring in real time in order to adjust the process parameters so that the quality of the product can be assured. The decision of the transition from one step to the following or a parameter adjustment is performed at defined points (points in the process where the transition decision is made) and based in defined criteria (information in real time that triggers the decision). Generally, this decision strategy alters the quality assurance of the product from fixed controls at the end of the batch manufacturing, to adaptive controls which are controlled during the manufacturing process so that the desired characteristics are attained more efficiently. PAT implementation by the industry contributes to a better quality risk management, as there is a higher process understanding, predicting failures in the system allowing for their correction before the occurrence.[23]

Hence, the process is well understood when all the variability sources are identified and explained, the variability is managed by the process and the product quality attributes can be foreseen with confidence and precision. Knowledge of the process is inversely proportional to risk. The focus on process understanding may reduce validation load, providing more options to justify and qualify the systems destined to monitor and control the chemical, physical and biological attributes of the materials and processes.[23]

PAT possesses two main components: a set of scientific principles and tools that promote innovation and a regulatory strategy to implement that innovation.

PAT contributes to QbD as an approach to reduce end of process testing and promote real time release. PAT application should be evaluated taking into account the operations performed at the site and all the advantages that it could bring. PAT application requires the appropriate combination of PAT Tools. These tools are:

- Multivariate tools for design, data acquisition an analysis;
- Process analysers;
- Process Control Tools;
- Knowledge Management and Continuous Improvement Tools.[11]

These tools can be applicable to a single operation or manufacturing process or it quality management process. The control strategy and the parameter analysis decision are based on process understanding that is generated during product design and the routine operations of the process or production unit. The three steps: design, analyse and control ensure that the product CQAs are consistently followed.[11]

In order to understand the process, as that is a fundamental requirement for PAT, it is necessary to apply quality risk management tools. The identification of the critical variability sources is performed by risk assessment that stands on the information given by PAT tools. Once the variability sources are identified, the application of risk reduction strategies is necessary.[11]

The implementation of process control strategies involves a higher operational complexity that requires the investment in facilities, equipment and personnel. On the other hand, PAT can result in the elimination of unnecessary monitoring and control. The adoption of these control strategies will promote changes in the development of the manufacturing, analytical, quality and regulatory processes.[11]

2.6.1.1. PAT Tool: Near Infrared Spectroscopy

NIRS is a fast, non-destructive method of analysis of any matrix. This analysis covers the wavelength from the medium infrared to the visible part of the spectra, i.e., between 780-2526 nm, which corresponds to a wavelength of 12820–3959 cm^{-1}. The absorption bands in this region are related with the overtones and combinations of fundamental vibrations of the functional groups: –CH, –NH, –OH and –SH.[23]

These bands are typically broad, overlapping and around 10 to 100 times weaker than its correspondent absorption in the MIR Spectra. These characteristics restrict the sensitivity of the method, needing the chemometric processing data to relate the spectra information with the sample characteristics. However, the low absorption coefficient allows high

penetration depth and, thus, a regulation according to the sample thickness. This can be viewed as an analytical advantage, as it allows the direct analysis of strongly absorbing and even highly scattering samples, such as turbid liquids or solids in either transmittance or reflectance mode without further pre-treatments.[23]

The dual dependence of the analytical signal on the chemical and physical properties of the sample, resulting from absorption and scatter effects, can be useful to be used to perform chemical and physical analysis from one single measurement. However, if not the analytical target, scatter effects in the NIR Spectra, resulting from physical sample variations, may also pose some analytical problems. In these situations, they need to be considered in the calibration process as "interfering parameters".[23]

NIR Spectrophotometer is generally composed of a light source, a monochromator, a sample holder or a sample presentation interface, and a detector, allowing for transmittance or reflectance measurements. The light source is usually a tungsten halogen lamp, since it is small and rugged. Detector types include silicon, lead sulphide (PbS) and Indium Gallium Arsenide (InGaAs). Silicon detectors are fast, low noise, small and highly sensitive from the visible region to 1100 nm. PbS detectors are slower, but very popular as they are sensitive from 1100 to 2500 nm and provide good signal-to-noise properties. The most expensive InGaAs detector combines the speed and size characteristics of the silicon detector with the wavelength range of the PbS detector.[23]

Since NIR Spectra are typically composed of broad overlapping , so that ill-defined absorption bands containing chemical and physical information of all sample components, the analytical information is multivariate in nature and, therefore, hardly selective. To perform qualitative or quantitative NIR analysis, meaning that it relates spectral variables to proprieties of the component, mathematical and statistical methods (including chemometrics) are required, so that they help to extract significant information and reduce interfering parameters.[23]

Before any quantitative analysis of the NIR spectrometer, it should be calibrated using multivariate methods. The calibration process involves the following steps:

1- Selection of a representative set of samples for the calibration;

2- Acquisition of spectra and reference values determination;

3- Multivariate modelling so that it relates the spectra variations with the reference values of the component;

4- Model validation by cross validation, set validation or external validation.[23]

The most frequently used methods for multivariate analysis are Principal Component Regression (PCR) and Partial Least Squares (PLS) Regression. PCR uses the principal components provided by PCA to perform the regression on the sample property to be predicted.[23]

NIR Spectroscopy possesses a high number of advantages when compared with other analytical methods, and thus offers many interesting perspectives in the analysis of pharmaceutical products. The scientific ground of this technology has been established to many different applications and justified by a great number of publications. However, in the highly regulated pharmaceutical area, an analytical method is only useful in routinely applications if it is approved by the regulatory authorities. European and US Pharmacopoeas possess monographs for NIR techniques, although CHMP refers that the reference to this monograph is not enough, as only the NIR process descriptions is insufficient to justify the use of this method in AIM and alterations requests. These monographs refer to the suitability of the NIR instrumentation to the use in pharmaceutical analysis, centring on the operational and performance qualification, comprising the wavelength scale and repeatability as well as the output repeatability, the photometric linearity as well as the photometric noise.[23]

This method advantages are:

- Non invasive and destructive method;
- Does not require sample preparation, or only requires a minimum preparation. Solid samples can be directly measured without pre-treatment if a suitable equipment is used;
- The measurement and the result delivery are quick. NIR equipment and chemometrics developments, as well as its usage in line with computers, allow the real time extraction of the sample analytical information;

- There is no need to use reagents or auxiliary materials to prepare the samples and the technique automation results in a higher yield, which reduces the analytical costs and its amortization;
- A simple spectra can allow the simultaneous analysis ir various components;
- This technique allows the determination of physical properties of the components. The influence of these parameters in the NIR spectra allows the quick determination of properties such as density, viscosity and particle size;
- Due to the various optical force of the materials to the equipment robustness of the NIR equipment, the NIR instrumentation is the most adequate to the in process control in the production areas;
- The optical fibres are strong and robust sensors to the "on-line", "at-line" and "in-line" process analysis;
- The NIRS results are comparable in terms of precision to the remaining analytical techniques, being its precision higher as it does not need sample preparation.

This method disadvantages are:

- NIRS measurement are poorly selective, and thus need to use chemometric techniques to model the data and extract the relevant informations;
- There are no precise models to relate the interaction between the NIRS light and the component. As a result, the calibration is in many cases empirical;
- Robust and precise calibration models are hard to obtain, as its construction implies the usage of a high number of samples so that it comprises all the variations on the chemical and physical properties of the component;
- The need to embed the physical and chemical variability of the calibration samples implies the usage of different calibration models, as there are various types of samples and thus, various models for one component;
- As NIRS is a relative methodology, the construction of models for its use require the previous knowledge of the value for the target parameter that should be previously determined using a reference method;

- The technique is not very sensitive, so that can generally only be applied in main components;
- NIRS model construction requires a substantial investment, which can, however, be compensated by the transference of calibrations from the main equipment.[23]

2.6.2. Statistical Process Control

ICH Q8 and Q10 refer that processes should be established and maintained within a state of control, so that effective monitoring and control systems should be provided for increasing process performance and product quality and facilitate continuous improvement.

Statistical Process Control (SPC) aims to monitor the method/procedure performance on a continuing basis, detecting different types of unexpected results or if there are any significant changes in the process (trends or shifts) that need special attention.[24]

The sigma value is a metric that shows how well the process is performing. The lower the sigma, the lower the variation and the better the process is performing. The term six sigma (6σ) comes from the assumption that if one has six standard deviations between the process mean and the nearest specification limit, there will be practically no items that fail to meet specifications. A process that operates at six sigma level guarantees that 99,99966% of the process is defect free, which means 3,4 defects per million opportunities (DPMO). [24]

Statistical Process Control (SPC) concepts and methods are a key tool for the monitoring of the process performance over time and to verify that the process remains in a state of control as required by the guidelines above mentioned. This tool can be used for Continuous Improvement as well as to aid the prevention of problems in the process.

There are two types of variability:

- **Common cause** – that is a natural case of variability, management controllable and predictable by mathematics rules. This is unavoidable but can be reduced. This variability has low risk and low cost, as it is predictable and controlled and in statistical control.

- **Special cause** – this is an un-natural case of variability, that is operator controllable and mathematics do not apply. This variation is avoidable and can be eliminated, although it is high cost and high risk. This variability is not predictable, not controlled and not in statistical control. [24]

Being at a state of control means that process or product variables remain close to the desired values and that the only source of variation is "Common cause". Control charts are used to monitor CQAs and CPPs in order to detect the occurrence of events of "Special cause" so that the root cause could be found and long-term improvements are achieved when eliminating the causes of these events and improving the process and the applicable SOPs. [25]

SPC is different from automatic processes feedback control. These controls should be applied wherever possible to reduce variability in important processes and product variables in order to adjust the process and maintaining the process parameter within the desired range. SPC methods should be applied on the top of the processes and its automatic control systems to detect process behaviour that indicates the occurrence of special events, so that the cause for this events are determined and removed (and not simply compensated), so that the process is improved.[25]

A successful SPC program involves Management Leadership, as team approach that focuses on project-oriented applications, education of employees at all levels, emphasis on reducing variability, measuring success in quantitative terms and a mechanism for communicating successful results through the organisation.

Most nonmanufacturing processes have scrap, rework, and other non-value-added operations, such as unnecessary work steps and choke points or bottlenecks. A systematic analysis of these processes can often eliminate many of these non-value-added activities. Some ways to eliminate these activities are:

1. Rearrange the sequence of work steps;
2. Rearrange the physical location of the operator in the system;
3. Change work methods;
4. Change the type of equipment used in the process;
5. Redesign forms and documents for more efficient use;
6. Improve operator training;
7. Improve supervision;
8. Identify more clearly the function of the process to all employees;

9. Try to eliminate unnecessary steps;
10. Try to consolidate process steps.[26]

Control chart is the graphic representation of a characteristic of a process showing values of some statistic gathered from the characteristic, a centre line, and one or two control limits. It has two basic uses:

- to determine if a process has been operating in statistical control and
- to aid in maintaining as well as improving process control. [27]

Selection of proper SPC Control Charts is essential to the SPC implementation and success. It is important to determine the control chart to be used according to the data, situation and need. There are two types of control charts depending on the type of data:

- Variable Control Charts – designed to control product or process parameters which are measured in a continuous measurement scale. For this data, the primary charts used are X-bar, R and Individual.
- Attribute Control Charts – characteristics of a process which are stated in terms of classification (complies, nor complies) or number. These control charts are not as sensitive to variation as the variable control charts. However, when used properly, this can be very effective tools. Tools used are P-Charts, NP-Charts, C-Charts and U-Charts.[27]

These charts are often the best tools to achieve the process control and capability. The control charts are used to:

- detect special causes of variation in the process at the time they exist so that they can be easily identified and corrected;
- identify patterns of variation in the process which provide early indicators that the product will be defective;
- provide statistical limits which define the natural tolerance of the process, and are used to stabilize the process (or get the process in-control).

Standard use of SPC involves two phases, which maintain two distinct objectives. Phase I is where a set of data is gathered and analysed all at once in a retrospective analysis, constructing control limits to determine if the process was in control over the period in which the data was collected. In this phase, also, the reliability of the process and control limits over that period can be verified. This is

generally the first step, where the control charts help bringing the process into a control state. Phase II begins after the process is at a stable and in control state, with a set of data gathered under these conditions. This phase the control charts are used to monitor the process by comparing the sample statistic for each successive sample as it is drawn from the process with the process control limits.[25]

Implementation of SPC should take into account the type of data in order to select the most appropriate method, as according to Figure 1.

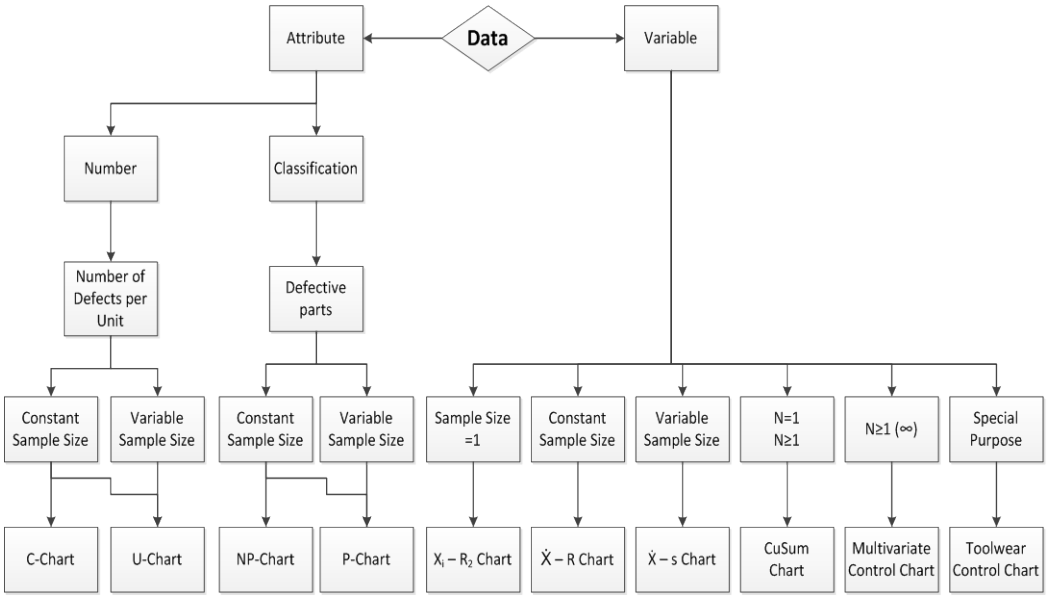


Figure 2 - SPC Control Chart Selection

Control charts contain a centre line that represents the average value of quality characteristics corresponding to the in-control state. There are two horizontal lines, called the upper control limit (UCL) and the lower control limit (LCL) that are chosen so that if the process is in control, nearly all sample points will fall between them. If the plot points maintain within the control limits, the process is assumed to be under control. However, if a point is outside of the limits, there is evidence that the process is not controlled, and investigation and corrective actions are required in order to eliminate the cause.[25,27]

Control charts are well accepted as they are a successful technique for improving productivity, as it will help to reduce scrap and rework. Control charts also prevent defects, as it helps to maintain the process under control and prevents unnecessary process adjustment, distinguishing between background noise and abnormal variation. They also provide information about process capability,

related with the value of important process parameters and their stability over time, which allows estimating the process capability.[26]

When dealing with a variable quality characteristic, it is necessary to monitor the mean value of the characteristic and it variability. Control of the process average or mean quality level is usually done with the control chart for means, or the control chart. Process variability can be monitored with either a control chart for the standard deviation, called the s control chart, or a control chart for the range, called an R control chart. The R chart is more widely used.[27]

If a CQA is normally distributed with a mean μ and a standard deviation σ, if $x1$, $x2$, . . . , xn is a sample of size n, then the average of this sample is

$$\bar{x} = \frac{x1 + x2 + \cdots + x\mathrm{n}}{n}$$

As $\bar{x}$ is normally distributed with mean μ and standard deviation

$$\sigma\bar{x} = {}^{\sigma}/_{\sqrt{n}}$$

Furthermore, the probability is 1 − α that any sample mean will fall between

$\mu + Z_{\alpha/2}\,\sigma\bar{x} = \mu + Z_{\alpha/2}\,{}^{\sigma}/_{\sqrt{n}}$ and $\mu - Z_{\alpha/2}\,\sigma\bar{x} = \mu - Z_{\alpha/2}\,{}^{\sigma}/_{\sqrt{n}}$

If μ and σ are known, the upper equation can be used to calculate upper and lower control limits on the control chart for sample means ($\bar{x}$ Control Chart). The term $Z_{\alpha/2}$ is usually replaced by three, so that three sigma limits are employed. The distribution of the characteristics is assumed to be normal. However, the above results are still approximately correct even if the underlying distribution is non-normal, because of the central limit theorem.

As in practice the values of μ and σ are not known, an estimation of these values is needed. These estimates should be based upon 20-25 samples. Suppose that m samples are available, the estimator of μ is the mean:

$$\bar{\bar{x}} = \frac{x1 + x2 + \cdots + x\mathrm{m}}{\mathrm{m}}$$

So that $\bar{\bar{x}}$ can be used as a centre line for the $\bar{x}$ Control Chart.

In order to construct the control limits, estimate σ is also needed, so we need to use the Range method. If $x1$, $x2$, . . . , xn is a sample of size n, then the range of the sample is the difference between the largest and smallest observations, that is:

$R = x_{max} - x_{min}$

If R_1, R_2, … R_m are the ranges of the m samples, the average range is:

$$\bar{R} = \frac{\mathrm{R1} + \mathrm{R2} + \cdots + \mathrm{Rm}}{m}$$

So, these terms can be used to construct the control chart:

UCL= $\bar{\bar{x}}$ + $A_2\bar{R}$

Center line= $\bar{\bar{x}}$

LCL= $\bar{\bar{x}}$ - $A_2\bar{R}$

Being A_2 a constant defined according to the sample size.

If the samples are monitored by plotting the sample ranges, then the control chart terms are:

UCL= $D_4\bar{R}$

Center line= $\bar{R}$

LCL= $D_3\bar{R}$

Being the constants $D_{3\ \text{and}}$ D_4 constants defined according to the sample size.

A control chart may indicate that a process is out of control when one or more points fall beyond the control limits or when the plotted points exhibit some non-random pattern of behaviour. If the control chart breaks one of these rules, the process is stated not to be under control:

1. One or more points outside of the control limits.
2. Two of three consecutive points outside the two-sigma warning limits but still inside the control limits.
3. Four of five consecutive points beyond the one-sigma limits.
4. A run of eight consecutive points on one side of the centre line.
5. Six points in a row steadily increasing or decreasing.
6. Fifteen points in a row in zone C (both above and below the centre line).
7. Fourteen points in a row alternating up and down.
8. Eight points in a row on both sides of the centre line with none in zone C.
9. An unusual or non-random pattern in the data.
10. One or more points near a warning or control limit.[26]

Although $\bar{x}$ and $\bar{R}$ Control Charts are widely used, sometimes it is desirable to estimate the process standard deviation directly, instead of using the range R –this leads to control charts for $\bar{x}$ and s, where s is the sample standard deviation.

These charts are used when the sample size *n* is moderately large or the sample number is variable.[26]

In order to set up this control chart, the sample average $\bar{x}$ and sample standard deviation must be calculated. If σ^2 is the unknown variance of a probability distribution, then a more precise estimator of σ^2 is the sample variance:

$$s^2 = \frac{\sum_{i=1}^{n}(x_i - x)^2}{n-1}$$

However, the sample standard deviation is not an unbiased estimator of σ. If the distribution is normal, then s actually estimates $c_4\sigma$, where c_4 is a constant value that depends on the sample size *n*. So, the standard deviation of s is $\sigma\sqrt{1-c4^2}$. So this information can be used to establish control charts on $\bar{x}$ and σ. The control levels can also be calculated by:

UCL= $c_4\sigma + 3\,\sigma\sqrt{1-c4^2}$

LCL = $c_4\sigma - 3\,\sigma\sqrt{1-c4^2}$

Two constants can be defined:

$B_5 = c_4 + 3\sqrt{1-c4^2}$

$B_6 = c_4 - 3\sqrt{1-c4^2}$

Consequently, the parameters for the Control Chart become:

UCL= $B_5\sigma$

Center line = $c_4\sigma$

LCL= $B_6\sigma$

B_5 and B_6 are constants defined in Annex 1.

If there is no standard value given for σ, then it must be estimated by analysing past data. Suppose that *m* preliminary samples are available, each of size *n*, and s_L rhe standard deviation of the L^{th} sample. The average of the m standard deviation is:

$$\bar{s} = \frac{1}{m}\sum_{i=1}^{m} s_i$$

The statistic $\bar{s}/c_4$ is an unbiased estimator of σ. Therefore, the parameters of the s chart would be

UCL= $\bar{s} + 3\,\frac{\bar{s}}{c4}\sqrt{1-c4^2}$

LCL = $\bar{s} - 3\,\frac{\bar{s}}{c4}\sqrt{1-c4^2}$

Two constants can be defined:

$B_3 = 1 - \frac{3}{c4}\sqrt{1 - c4^2}$

$B_4 = 1 + \frac{3}{c4}\sqrt{1 - c4^2}$

Consequently, the parameters for the Control Chart become:

UCL= $B_4\,\bar{s}$

Center line = $\bar{s}$

LCL= $B_3\bar{s}$

As $B_4 = B_6/c_4$ and $B_3 = B_5/c_4$ and $\bar{s}/c_4$ is an estimator of σ, the control limits for the $\bar{x}$ chart may be defined as:

UCL= $\bar{\bar{x}} + \frac{3\bar{s}}{c4\sqrt{n}}$

Center line = $\bar{\bar{x}}$

LCL= $\bar{\bar{x}} - \frac{3\bar{s}}{c4\sqrt{n}}$

As the constant $A_3 = 3/(c4\sqrt{n})$, the chart parameters can be:

UCL= $\bar{\bar{x}} + A_3\,\bar{s}$

Center line = $\bar{\bar{x}}$

LCL= $\bar{\bar{x}} - A_3\,\bar{s}$

A_3 is a constant defined according to sample size.[26]

The Control Charts identified before are useful in phase I implementation of SPC, when the process is likely to the out of control and experiencing assignable causes that result in large shifts in the monitored parameters, as well as helping the process to be in a statistical control state. A major disadvantage of these control charts is that they only use information about the process contained in the last sample observation and it ignores the information given by the entire sequence of points, which makes these control charts insensitive to small process shifts, so that they are not so useful in Phase II monitoring. Alternative to these Control charts in this case is the CuSum Control Chart. This Control Chart directly incorporates all the information in the sequence of sample values by plotting the cumulative sums of the deviations of the sample values from a target value. Because it combines information from several samples, CuSum Charts are particularly more effective than the X-Charts for detecting small process shifts. Also, they are particularly effective in samples of size n=1.[26]

As many quality characteristics cannot be conveniently represented numerically, they are normally classified in each item inspected as either conforming or nonconforming to the specifications on that quality characteristic. So, there are also attribute Control Charts.

P-Chart relates to the fraction of nonconforming or defective product produced by a process.

NP-Chart relates to the number of nonconforming or defective product rather than the fraction nonconforming.

C-Chart relates to the nonconformities per unit, in which a unit can attain more than one defect.

U-Chart relates to the nonconformities per unit, which is useful in situations where the average number of nonconformities per unit is a more convenient basis for process control.

Attributes charts are generally not as informative as variables charts because there is typically more information in a numerical measurement than in merely classifying a unit as conforming or nonconforming.[26]

Control charts are one of the tools to use in a SPC program, but there are six more tools that can be applied through the process. These are:

- **Histogram -** This is a graphical representation of the distribution of data. It is an estimate of the probability distribution of a continuous variable.
- **Check Sheet -** This can be used in the early stages of the process to collect historical or current operating data about the process. There should be a clear definition of what data is going to be collected, the operation number, the operator, date and any other variable that can be useful in the diagnosis of poor performance.
- **Pareto Chart -** This is a frequency distribution (or histogram) of attribute data arranged by category. These charts are usually used in the analysis if the frequency of the defects, so to know which defects should be controlled first (not the most critical defects, but the ones occurring more frequently).
- **Cause and effect diagram –** This tool can be used in identifying potential causes for a defect, error or problem. The diagram should be constructed on the basis of the problem or effect to be analysed, specifying the major potential categories. In these categories there should be an analysis of which should be the

possible causes. This can be an extremely powerful tool, as an highly detailed diagram can serve as an effective problem solving aid.

- **Defect concentration diagram –** This is a picture of the unit showing all its relevant views. Then the various types of defects can be drawn on the picture and the picture is analysed in order to determine whether the location of the defects shows any useful help on the potential causes of the defect.
- **Scatter diagram –** It is a useful plot for identifying a potential relationship between two variables by the shape of the diagram. Also, a regression modelling can be used in these diagrams.[26,27]

These tools comprise all the technical aspects of the SPC program, which are not the only factor needed for a successful SPC implementation. The proper development of SPC programs can create an environment in which all individuals seek continuous improvement in quality and productivity. This environment is best developed when management becomes involved in the process. Once this environment is established, routinely application of these tools becomes part of the usual routine.

2.7. Process Analysis

ICH Q10 main goals are achieving product realisation, establish and maintain a state of control and facilitate continual improvement.

Robustness is defined as the ability of a process to demonstrate acceptable quality and performance while tolerating variability in inputs. It is a function of both formulation and process design. Together with SPC and PAT it supports Operational Excellence of the process. Process robustness is a tool within manufacturing, production and methods for evaluating processes, quantifying the risk within the process, identifying and monitoring Six Sigma projects and setting objectives for senior management. Performance and variability are factors impacting robustness and may be managed through process design and product composition.[24]

Robustness is a function of both formulation and process design. Formulation design variables include the qualitative and quantitative composition of raw materials, both API and excipients. Process design variables include the process selected, the manufacturing and sequence or steps, the equipment settings such as speed and feed rates, and environmental conditions.[28]

Quality performance is managed by the presence of:

- Expertise in how to use systems, technology and workflows;
- Workflow in the organisation with interaction, cooperation, projects and control;
- Focus on tasks and priorities, opportunities, strategy and tactics;
- Science and Technology, with Paradigm Changes, Automation and Continuous Improvement.

Process Control should be based on the knowledge of the process and the quality system, understanding the processes so that quality metrics can be used successfully. When a process reaches the state of control it means that:

- the process performance is on target and ensures unit for unit consistent product quality;
- cost of failure is minimal through continuous improvement;
- Cost of detection is well balanced and founded on process understanding and process design for quality;
- Cost of prevention is minimal and safeguarded by QRM.[24]

Performance and variability are factors impacting robustness and may be managed through process de sign and product composition. Elements of product composition for consideration might include the choice of API forms, as some API forms are more robust than others, and the choice of excipients, including their grades and concentrations.

One of the ways to manage process performance and variability is through the choice of the manufacturing technology. Setting appropriate parameter ranges for a robust process requires consideration of the manufacturing technology selected. Well-designed processes reduce the potential for human mistakes, thereby contributing to increased robustness. During Process development, both the inputs and outputs of the process are studied with the purpose of determining the CQAs and CPPs as well as the tolerance of the parameters and how to control them. Process characterization during development phase aims to increase the process knowledge and understanding as well as the relationships of the parameters to the attributes. The knowledge available for a specific product and process, including CQAs and CPPs, process capability, manufacturing and process control technologies and the quality systems infrastructure is referred to as the Manufacturing Science underlying a product and process.[28]

Development of comprehensive manufacturing science for the product will produce the process understanding necessary to the definition of the relationship between a CPP and a

CQA. Often the relationship is not directly linked within the same unit operation or even the next operation. The impact of the starting materials, manufacturing equipment control and degree of automation needs also to be considered and understood. The objective of a well characterized process is to transfer a robust process which can be demonstrated with a high level of assurance, to consistently produce product meeting predetermined quality criteria when operating within the defined limits.[28]

In a robust process, CPPs have been identified and characterized so that the process can be controlled within defined limits for those CPPs. The NOR of the process is positioned within the PAR (Proven acceptable range) for each of the CPPs. The PAR is a function of the process and reflects the range over which a parameter can vary without impacting CQAs. A process that operates consistently in a narrow NOR demonstrates low process variability and good process control. The ability to operate in the NOR is a function of process equipment, defined process controls and process capability. [28]

When the product is transferred from development to Manufacturing, it will most likely encounter a much wider range of variation on the parameters than seen in development. It is upon transfer to Manufacturing that assessment of the true process capability and robustness as well as any process improvement should begin. Manufacturing yields a large amount of process data that should be periodically analysed to assess process capability and robustness and to prioritize improvement efforts. The data should be reviewed during the improvement effort to identify correlative relationships. Feedback to development may occur during these activities to further build quality into the design process.

The state of robustness should be monitored using SPC charts combined with capability index calculations. [28]

After verifying that the process is in statistical control, the process capability can be calculated. Process capability refers to the uniformity of the process, providing an assessment as to what extent the process is capable of meeting specifications and other requirements. The process capability can be monitored in order to adjust the process, being this a true process capability study, as interferences can be made about the stability of the process over time. Process Capability can also be calculated by measuring the CQAs by analysing the samples with no direct observation of the process or time history of production, then the study is more properly called product characterization. In a product characterization study we can only estimate the distribution of the product quality characteristic or the process yield (fraction conforming to specifications); we can say nothing about the dynamic behaviour of the process or its state of statistical control.

Process capability analysis is a vital part of an overall quality-improvement program. Among the major uses of data from a process capability analysis are the following:

1. Predicting how well the process will hold the tolerances;
2. Assisting product developers/designers in selecting or modifying a process;
3. Assisting in establishing an interval between sampling for process monitoring;
4. Specifying performance requirements for new equipment;
5. Selecting between competing suppliers and other aspects of supply chain management;
6. Planning the sequence of production processes when there is an interactive effect of processes on tolerances;
7. Reducing the variability in a process, thus, process capability analysis is a technique that has application in many segments of the product cycle, including product and process design, supply chain management, production or manufacturing planning, and manufacturing.[24]

The $\bar{x}$ and $\bar{R}$ Control Charts can provide information about the performance of the process or process capability. The Process Capability Ratio (PCR) C_p is calculated by the following formula:

$$Cp = \frac{\text{USL}-\text{LSL}}{6\sigma},$$

which relates to the allowable process spread and should be as large as possible. This index can only be used if the CQA has a normal distribution, the process is in statistical control and if the process mean is centred between the lower and upper specification limit. Thus, the Cp ratio simply measures the spread of the specification relative the six sigma spread in the process. This situation can be more accurately defined by defining a new index (Cpk) that takes centring into account:

$C_{pk} = \min\ (C_{pu}, C_{pl})$, being $C_{pu} = \frac{USL-\bar{x}}{3\sigma}$ and $C_{pl} = \frac{\bar{x}-LSL}{3\sigma}$

Although Cpk takes the mean centring into account, it still cannot provide an adequate measure of process centring, so that a large value of Cpk does not provide information about the location of the mean in the tolerance interval USL-LSL. The Cp and Cpk indices are appropriate measures of progress for quality improvement situations when reduction of variability is the guiding factor and process yield is the primary measure of a success.

However, they are not related to the cost of failing to meet customers' requirement of the target.

Unalike Cp and Cpk, Cpm index takes special attention on the loss in products worth when one of product's characteristics deviates from the customers' ideal value T. The index is geared towards measuring the ability of a process to cluster around the target, and reflects the degrees of process targeting (centring), incorporating the variation of product items relative to the target values and specification limits which are present in a factory. The index is defined as:

$$Cpm = \frac{\mathrm{USL}-\mathrm{LSL}}{6\sqrt{\sigma^2+(\mu-T)^2}},$$

The index Cpmk (motivated by the structure of Cpk (1)') alerts the user whenever the process variance increases and/or the process mean deviates from its target value. The index Cpmk has been referred to as the third-generation capability index, and is defined as:

$$Cpmk = \min\left(\frac{\mathrm{USL}-\mu}{3\sqrt{\sigma^2+(\mu-T)^2}}, \frac{\mu-\mathrm{LSL}}{3\sqrt{\sigma^2+(\mu-T)^2}}\right)$$

These indices are effective tools for process capability analysis and quality assurance. Two basic process characteristics: the process location in relation to its target value, and the process spread (i.e. the overall process variation) are combined to determine formulas for these capability indices. The closer the process output is to the target value and the smaller is the process spread, the more capable the process is. The first feature (closeness to the target) is reflected in the denominator while the second one (the process spread) appears in the numerators of these four indices. In other words, the larger the value of a PCI, the more capable is the process.[26,29]

When the distribution is small spread, so that it is close to target, the Cp will be higher. Otherwise, if the mean is far from USL and LSL and the distribution is small spread, the distribution is centred and Cpk will be higher. Cp value and definition is defined according to the sigma values it represents and the process yield that can be obtained. So, the values should be[8]:

Cp	**Sigma Level**	**Yield**	**Proportion of defective units**

0,33	1	68,269%	31,73%
0,67	2	95,44%	4,55%
1,00	3	99,73%	0,27%
1,33	4	99,9937%	0,0063%
1,67	5	99,9999426%	0,574ppm
2,00	6	99,9999998%	0,002ppm

Table 1 – Cpk values according to Sigma Level

Typical sources of variability may include process equipment capabilities and calibration limits, testing methods variability, raw materials, human factors for non-automated processes, sampling variability and environmental factors within the facility.

It is not necessary to take a process to the edge of failure to determine the upper and lower limits of a defined process. The defined limits, however, should be practical and selected to accommodate the expected variability of parameters, while conforming to the CQA acceptance criteria.[28]

3. Injectables Line

Labesfal, Laboratórios Almiro, S.A. is a 100% subsidiary of the German company, Fresenius Kabi AG. Fresenius Kabi AG is a business division of Fresenius SE, a global health care group with products and services for dialysis, hospital and homecare.
Labesfal's site integrates 4 units of production installed in 3 independent buildings. Unit 1 is where Penicillin's are produced. Unit 2 and 3 is where the following pharmaceutical forms are produced: sterile solutions (small and large volume), solids dosage forms, semi-solids and liquids. Unit 4 is where Cephalosporin's are produced.

3.1. Process Characterization

The Small volume Parenterals production in glass ampoules takes place in Production Unit 2. The manufacturing process consists on the dissolution of the API in water for injections, on a vessel, at room temperature. The excipients are added subsequently. The mixture is agitated and the pH is adjusted. Water for injections is added to reach the final volume. The solution is agitated for further minutes depending on the product that is manufactured. The primary packaging materials are glass ampoules. The primary filling is performed with an adequate machine for filling and sealing the Ampoules under Grade A environment. The ampoules are subsequently sealed by heat and mechanical strength, sterilized in autoclave, inspected and labelled with the batch number and expiry date. Finally, they're packed into boxes, together with packaging leaflet, marked with the batch number and expiry date, as detailed in the below Process Flowchart (Figure 2).

Regarding Legacy products, the current state are long and varying lead times, with low utilization and quality by inspection with high scrap. A strategy should be defined, with realistic objectives and a highly detailed plan. This should be a step in order to increase product and process understanding for these products. The execution and evaluation if the plan should lead to a Desired State with shorter lead time with improved utilization of the process control and reduction of variability as well as a higher process understanding. These can contribute to predictable product quality and ultimately to real time release of the products.[8]

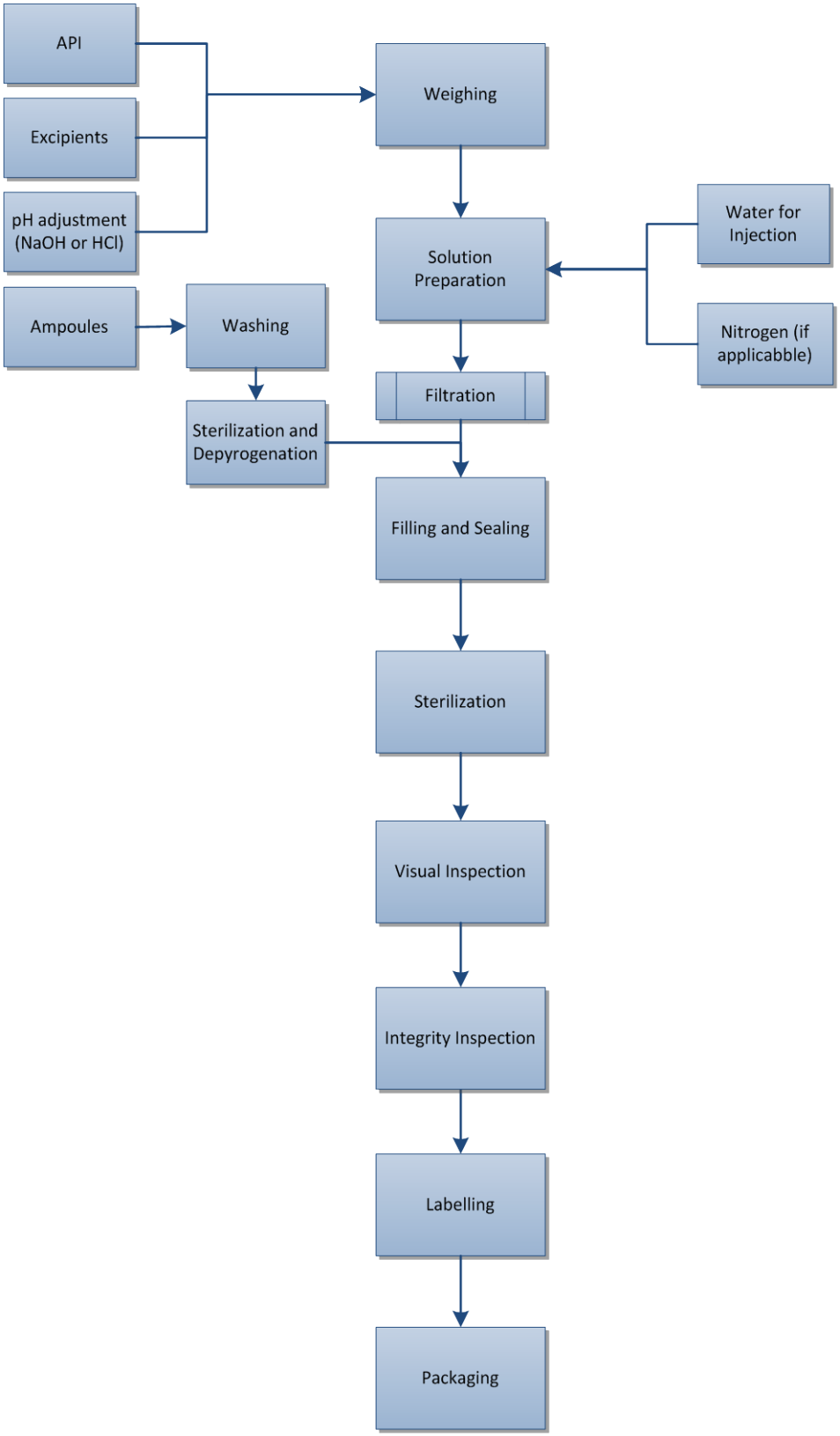


Figure 3 - Process flowchart

In order to verify which features can influence the quality of the finished product, the following Ishikawa diagram was developed.

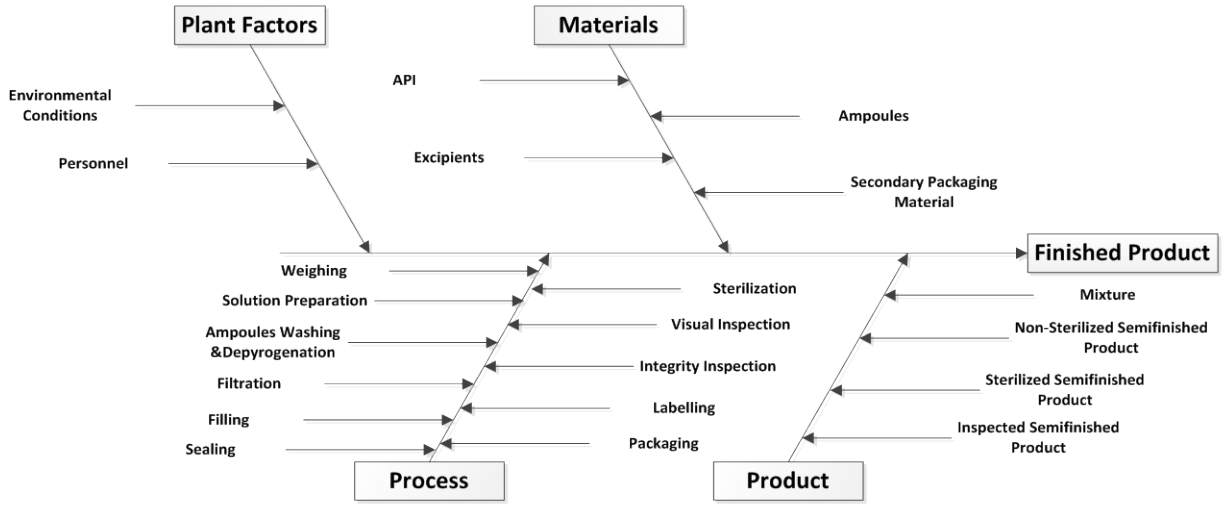


Figure 4 . Ishikawa diagram for the Process Flow

Process Steps are described below, as are the parameters that can be important to evaluate in each step.

3.1.1. Weighing

APIs and Excipients should be tested according to its specifications, and only approved materials can enter weighing rooms.

Weighing is performed in a separated area under Laminar Air Flow (LAF) with Class D background.

3.1.2. Solution Preparation

After Weighing, APIs and Excipients are transferred to the production area. Preparations room is class C. In this room there are several reactors (various capacities) similar to each other.

The reactor and line are cleaned by the System CIP/SIP (Clean-in-Place/Sterilization-in-Place). This program has to be successful in order to begin the preparation of the mixture. It begins adding a small quantity of water for injections, which should be around 30°C, as the API can be thermo labile. Then, the Excipients and API are added and the stirring begins. The remaining quantity of water is added after the total dissolution of the materials added.

The stirring can be influenced by:

- **Time** – the time of stirring can influence the dissolution of the API and excipients.
- **Speed** – the speed of stirring can influence the dissolution of the API and excipients as well as the powder disaggregation.

3.1.3. Filtration

The solution is filtered through a 0,22 µm filter (filter sterilization) when leaving the reactor towards the filling machine. This filter should be integrity testes before and after each usage.

3.1.4. Ampoules

The primary packaging material for our product is the ampoules. Ampoules may be clear or amber, manufactured with type I glass, type C form (acc. to ISO 9187-2).
Ampoules glass must comply with European Pharmacopoea requirements for type I glass containers and, if they are manufactured with amber glass, it should also comply with light transmittance.

3.1.5. Ampoules Washing

Ampoules' washing is performed in a rotary washer machine. This machines CPPs are:

- **Water Temperature** – This parameter can influence the efficiency of the washing;
- **Water Pressure** – this parameter will influence the correct and efficient washing of the ampoules;
- **Washer Velocity** – this parameter can influence the efficiency of the washing as well as the efficient processing, as if the washer is too fast, more ampoules can break on the process.

3.1.6. Ampoules Depyrogenation

After washing, the ampoules are continuously conveyed to the tunnel, sterilized, depyrogenated and then cooled before being transferred to the filling and sealing station. The key parameters are:

- **Conveyor belt velocity** – this parameter can influence the stability of the ampoules in the tunnel and also the time that they spend in the tunnel, affecting the exposure to the sterilization temperature.
- **Chamber temperature** – the temperature should be high enough so that the ampoules are efficiently sterilized and depyrogenated and the value of F_H is sufficiently high to assure the accomplishment of the process.

3.1.7. Filling

After cooling, the ampoules are directed to the filling and sealing line. The Filling process can be influenced by:

- **Solution flow** – the solution should flow properly in order to be filled in the ampoules. Filling needles depend on product flow.
- **Volume to fill** – The correctness of the volume will influence the intended use on the dosage form, as it can influence the dosage uniformity.

3.1.8. Sealing

The sealing process can be influenced by:

- **Flame Temperature** – the flame will melt the glass and seal the ampoule. If the flame temperature is not adequate, the sealing may be compromised.
- **Ampoules Height** - it is determined by the height of the flame and will influence the ease of opening.

3.1.9. Sterilization

Ampoules are now placed in trays and, depending on the product, may be sterilized in the autoclave by hot steam. This step assures the use of the finished product.

- **Time** – This parameter determines the time that the product remains under the 121°C temperature. Together with the temperature it will influence the F_0 of the sterilization process. According to European Pharmacopoea (EP) the process should take at least 15 minutes.
- **Temperature** – This parameter is the key to the sterilization process, as high temperatures assure the absence of microorganisms According to EP it should be at least 121°C, unless the process is demonstrated to possess the same lethality rate.

3.1.10. Visual Inspection

Visual inspection is performed in an automated machine. The machine contains a light-transmission double-check system for detecting particles in ampoules. It uses a Static Division (SD) system that divides the photo detector into independent parts that span a detection window from the base of the ampoule to just below the meniscus. First, the container spins at a specified speed. As the vials spins, the liquid forms a vortex that imparts movement to the insoluble particles. When the vial stops through the application of brakes, the vortex collapses, lifting and rotating the suspended particles. This image is projected into the SD sensor that verifies the variation of the intensity of the transmitted light.

This machine inspects the following defects: particles, volume and cosmetic defects in the head of the ampoule. The inspection process can be influenced by:

- **Rotation Speed -** this parameter is defined so that it can optimize the particles to suspend.
- **Brake Position -** this parameter affects meniscus recovery and the timing between the end of spin and the inspection.
- **Light Intensity –** this parameter defines the intensity of the light that will illuminate the solution.

- **Sensitivity –** this parameter defines the threshold of particle detection, differentiating the signal from the noise.

3.1.11. Integrity Inspection

Integrity inspection is performed in an automated machine by High Voltage Leak Detection (HVLD). In this machine, High voltage is applied to a hermetically sealed container made of non-conductive material (Glass). If pinhole or crack is present on the ampoule, the discharge current flows into the ampoule through the pinhole or crack. The defective ampoule is detected by the differential of the current flow as measured in the intact ampoule. This detection can be influenced by the Product conductivity.

3.1.12. Labelling

Labelling is performed in an automated machine that imprints the batch number and expiry date on the label, as well as possesses a sensor that detects the ring code colour and label presence.

The parameters that can influence the labelling process are:

- **Label –** The correctness of the label placement is essential to the identification of the product, influencing its quality.
- **Ring quality & quantity –** The correctness of the ring colour code is essential to the identification of the product to be labelled, as the colour code is exclusive to one product.
- **Bar code –** The correctness of the bar code is essential to the correctness of the label that will identify the product.
- **Batch & Expiry date printing –** The correctness of the printing will allow the correct traceability of the batch.

3.1.13. Packaging

Packaging is performed in an automated machine that forms the blister tray, presses the ampoules in the blister tray and places the trays in the carton box with the leaflet.

The parameters that can influence the labelling process are:

- **Blister tray formation –** The correct formation of the blister tray will influence the ampoule placing in the tray and thus, the number of ampoules that will be on the tray.
- **Ampoule tray colocation & pressing –** The correct ampoule placing in the trays (with its colocation and pressing) will ensure the completeness of the tray and that no ampoule is lost or broken during the remaining of the process.
- **Ampoule presence –** This sensor detects if the ampoules are correctly placed in the trays, thus ensuring that only trays with the correct number of ampoules are packaged.
- **Tray cut –** The correct cut of the tray ensures that the tray is well shaped so that it can have the correct number of ampoules and that they can be well place in the tray.
- **Leaflet -** The correctness of the leaflet (detected by bar code sensor) and its placement is essential to the completeness of the packaging.
- **Carton Box -** The correctness of the carton box (detected by bar code sensor) and its correct formation is essential to the correctness of the packaging.
- **Batch & Expiry date printing –** The correctness of the printing will allow the correct traceability of the batch.

These parameters will be evaluated later together with the CQAs.

3.2. CQAs and CPPs Definition

CQAs should be defined based on the target drug profile, meaning that these are quality characteristics of the drug that must be kept within appropriate limits to ensure the desired product quality. For each CQA, an analysis of the potential CPPs and potential Critical Material Attributes (CMAs) is conducted.

This is performed so that each process step is evaluated and is identified each operating parameter or raw material that has the potential to affect a CQA. These identified parameters or raw material should therefore be controlled or monitored in order to ensure that the product reaches the desired quality.[4]

CQAs are quantifiable properties of an intermediate or final product considered critical for establishing the intended purity, efficacy and safety of the product, which means that the attribute must be within a predetermined range to ensure final product quality. Even though there are some non-quality specific attributes that may be identified, as some business related attributes, they are outside the scope of the CQAs.[28]

CPPs are process inputs that, when varied beyond a limited range, has a direct and significant influence on a CQA. The failure to stay within a determined range of CPP leads to a probable failure of a CQA. Parameters that affect business objectives or workers safety are not considered CPPs. [28]

3.2.1. Desired Product Quality

CQAs for injectables should be related with the following product characteristics:

- Purity – assure that the compounds that are present in the solution are the ones that should be;
- Safety – the absence of these CQAs would cause harm to the patient;
- Strength – must be present to assure the effectiveness of the product;
- Identity – assures that the product is what it is supposed to be.[30]

The Quality Target Product Profile is:

- Suitable for its intended use – parenteral dosage form;
- Within specifications;
- Sterile and Endotoxin free;
- Stable.

To achieve the QTTP, the Finished Product CQAs should be:

- Assay;
- Impurities;
- Particulate Contamination;
- Endotoxins;
- Sterility;
- Correct identification of product and batch number.

3.2.2. Risk Analysis

In order to verify in a detailed manner which features can influence the quality of the finished product, an Ishikawa diagram was developed for each CQA defined in 3.2.1. and the CPPs to be controlled were defined according to its influence on the CQA.

Plant factors such as Environmental Factors and Personnel are always considered, but will not be detailed as they are generally covered by GMPs and their influence can be minimized. Table 2 shows the cause-effect matrix between Unit Operations and CQAs.

CQAs	Unit Operations											
	Weighing	Solution Preparation	Filtration	Ampoules Washing	Ampoules Depirogenation	Filling	Sealing	Sterilization	Visual Inspection	Integrity Inspection	Labelling	Packaging
Assay	High	Medium	Low	Low	Low	Low	Low	Medium	Low	Low	Low	Low
Impurities	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Particulate Contamination	Low	Low	High	High	Low	Low	Low	Low	High	Low	Low	Low
Endotoxins	Low	High	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Sterility	Low	Low	Medium	Low	Medium	Low	Low	High	Low	Low	Low	Low
Correct Identification of Product and Batch Number	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Medium

Table 2 – Cause Effect Matrix between CQAs and CPPs

The High and Medium Risk Unit Operations will be evaluated regarding the parameters that can influence the CQAs.

3.2.2.1. Assay

The Ishikawa diagram for Assay is:

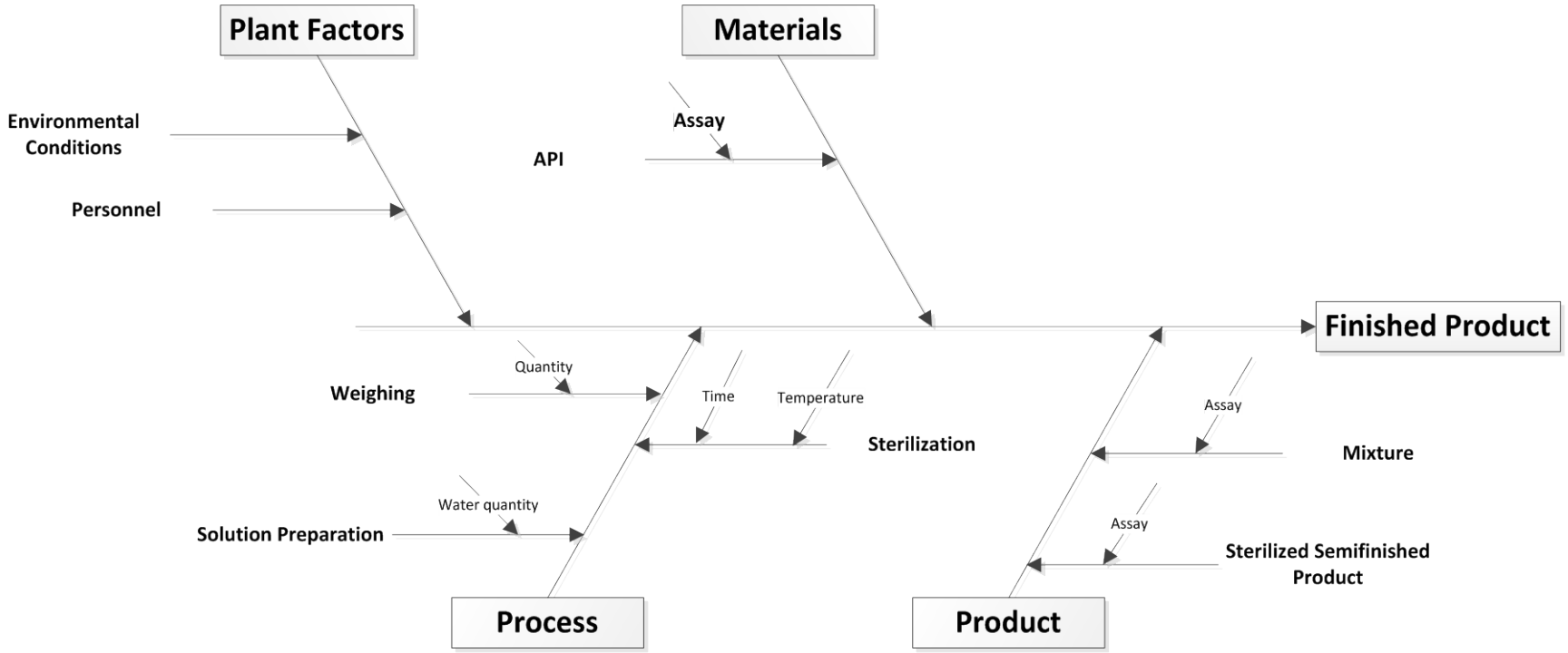


Figure 5 - Ishikawa Diagram for Assay

Assay should be controlled in the mixture and in the sterilized semifinished product in order to ensure that the process went as planned.

The CQAs and CPPs that influence the impurity Profile are summarized and justified below.

CQA	Branch	Step	CQA/CPP	Comments
Assay	Materials	API	Assay	API Assay will influence the Finished Product assay, as this is directly correlated with the quantity of API that is in the Finished Product.
	Process	Weighing	Quantities	The quantity of API weighed will determine the quantity of API that will be incorporated in the finished product and thus, its assay.
		Solution Preparation	Water Quantity	The quantity of water in the solution, is a function of the quantity of API so that it reaches a determined concentration and determines the Finished Product Assay.
		Sterilization	Time	Sterilization time and temperature are defined at the EP. These parameters, if they are too high, will potentiate the product degradation and decrease the Assay.
			Temperature	

Table 3 - CQAs and CPPs for Assay

3.2.2.2. Impurities

The Ishikawa diagram for the Impurities is:

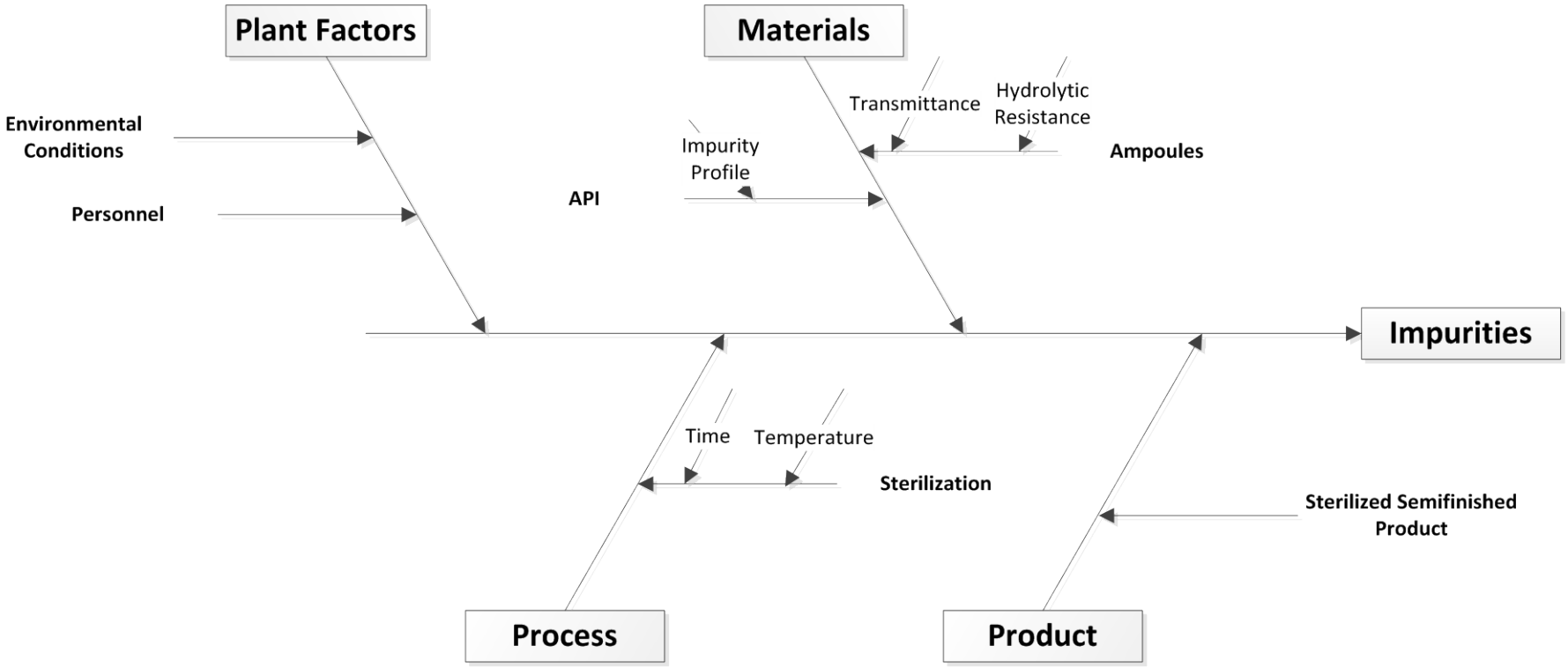


Figure 6 - Ishikawa diagram for Impurities

The Impurity profile should be monitored after the sterilization step as this step can highly influence the impurity profile and should be a known factor before the next steps take place.

The CQAs and CPPs that influence the impurity Profile are summarized and justified below.

CQA	Branch	Step	CQA/CPP	Comments
Impurities	Materials	API	API Impurities	API impurity profile will influence the level of impurities present in the finish product, as there are no steps in the production that can remove those substances.
		Ampoules	Hydrolytic Resistance	Ampoules must comply with EP type I glass requisites, as glass with lower hydrolytic resistance can react with the API and increase the impurity level.
			Light Transmittance	Ampoules must comply with EP amber glass requisites, as clear glass can let light pass which can react with the API and increase the impurity level.

CQA	Branch	Step	CQA/CPP	Comments
	Process	Sterilization	Time	The time in which a product is exposed to a high temperature will influence its degradation rate and can influence the Impurity profile of the product.
			Temperature	The high temperatures at which a product is exposed will influence its degradation rate and can influence the Impurity profile of the product.

Table 4 - CQAs and CPPs for Impurities

3.2.2.3. Particulate Contamination

The Ishikawa diagram for Particulate Contamination is:

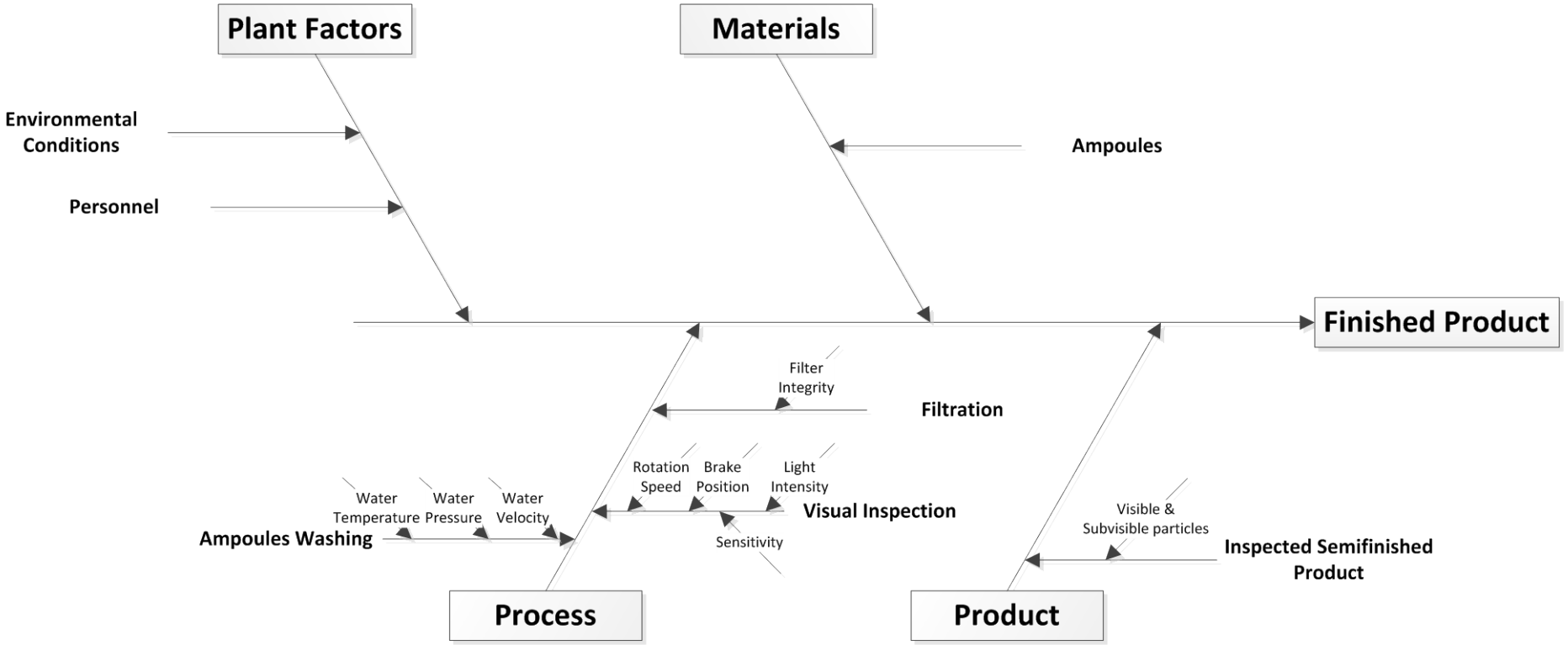


Figure 7 - Ishikawa diagram for Particulate Contamination

The CQAs and CPPs that influence the impurity Profile are summarized and justified below.

CQA	Branch	Step	CQA/CPP	Comments
Particulate Contamination	Process	Filtration	Filter Integrity	Filtration under 0,22 µm retains microorganisms and other contaminations of the product, minimizing the contamination at this point.
		Ampoules Washing	Water Temperature	These parameters will influence the efficiency of the ampoule washing and the removal of the contamination that might be present in the ampoules.
			Water Pressure	
			Water Velocity	
		Visual Inspection	Rotation Speed	These parameters influence the efficiency of the detection of visible and subvisible particles in the solution.
			Brake Position	
			Light Intensity	
			Sensitivity	

Table 5 - CQAs and CPPs for Particulate Contamination

3.2.2.4. Endotoxins

The Ishikawa diagram for Endotoxins is:

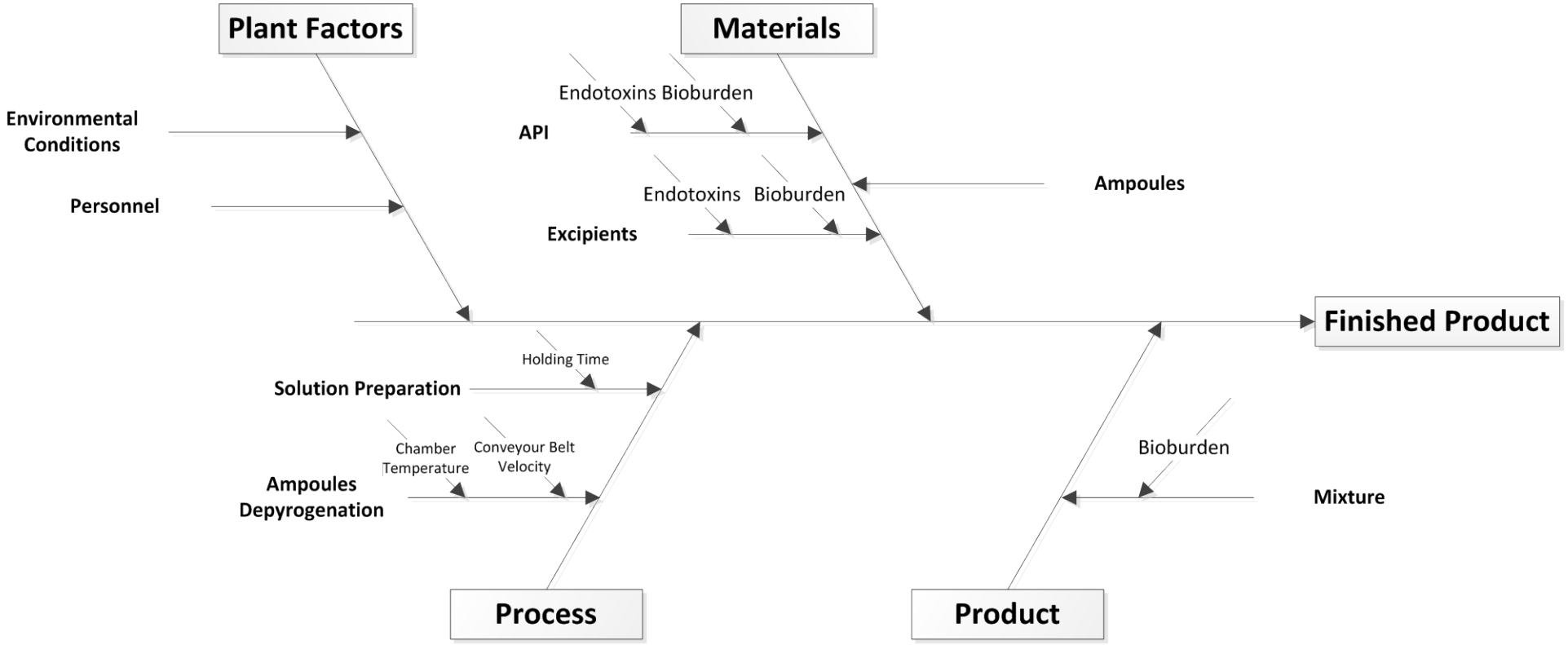


Figure 8 - Ishikawa Diagram for Endotoxins

Bioburden should be controlled in the mixture in order to assure that the endotoxin level will not increase.

The CQAs and CPPs that influence the impurity Profile are summarized and justified below.

CQA	Branch	Step	CQA/CPP	Comments
Endotoxins	Materials	API & Excipients	Bioburden	As endotoxins are present in the gram negative bacteria cell wall, the control of the bioburden in the raw materials in the solution is essential to maintain the low level of endotoxins.
			Endotoxins	If raw materials introduce a high level of endotoxins to the solution, this will be maintained through the process.
	Process	Solution Preparation	Holding Time	The time that elapses between the end of the preparation and the end of filling should not be too long, as the bioburden tends to increase, and, thus, the endotoxins present in the product.
		Ampoules Depyrogenation	Conveyour belt Velocity	The velocity of the conveyor belt influences the time at which the ampoules are expose to a determined temperature, and therefore, the microorganisms death.

CQA	Branch	Step	CQA/CPP	Comments
			Chamber temperature	The temperature at which the ampoules are subjected before filling influences the death rate of the microorganisms present in the ampoules.

Table 6 - CQAs and CPPs for Endotoxins

3.2.2.5. Sterility

The Ishikawa diagram for Sterility is:

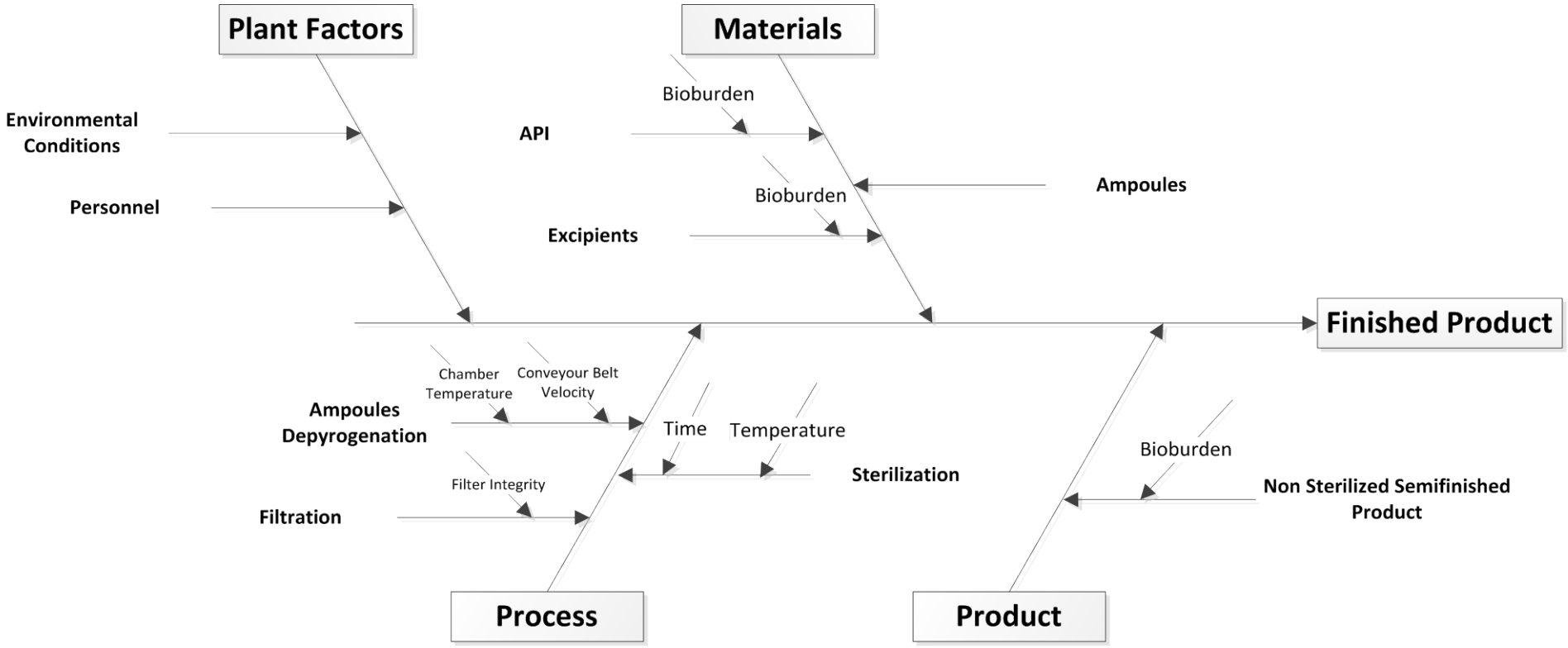


Figure 9 - Ishikawa Diagram for Sterility

Sterility should be tested after the sterilization step as this is the most important step at the assurance of the product sterility.

The CQAs and CPPs that influence the impurity Profile are summarized and justified below.

CQA	Branch	Step	CQA/CPP	Comments
Sterility	Materials	API & Excipients	Bioburden	The bioburden of the mixture and solution will be influenced by the bioburden of the initial materials that constitute this product.
	Process	Ampoules Depyrogenation	Conveyor belt velocity	The velocity of the conveyor belt influences the time at which the ampoules are expose to a determined temperature, and therefore, the microrganisms death.
			Chamber temperature	The temperature at which the ampoules are subjected before filling influences the death rate of the microorganisms present in the ampoules.
		Filtration	Filter Integrity	Filtration under 0,22 μm retains microorganism, minimizing bioburden in the solution and assuring that the process remains under controlled conditions.

CQA	Branch	Step	CQA/CPP	Comments
		Sterilization	Time	Sterilization time and temperature are defined at the EP. This parameters influence the death kinetic of the microorganisms present in the solution.
			Temperature	

Table 7 - CQAs and CPPs for Sterility

3.2.2.6. Correct Identification of Product and Batch Number

The Ishikawa diagram for the correct identification of product and batch number is:

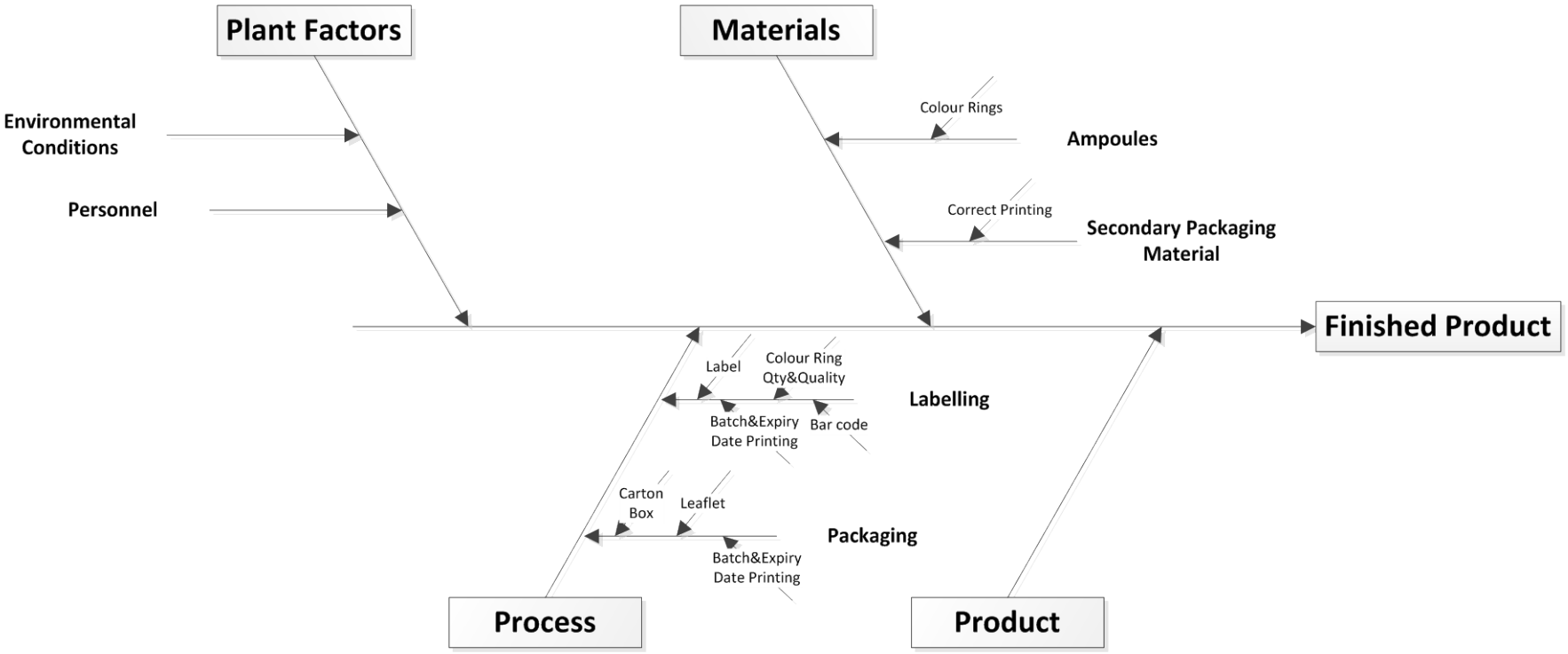


Figure 10 - Ishikawa Diagram for correct identification of product and batch number

The product must be correctly identified through all stages of the process. This is assured by the operators and equipments.

The CQAs and CPPs that influence the impurity Profile are summarized and justified below.

CQA	Branch	Step	CQA/CPP	Comments
Correct identification of product and batch number	Materials	Ampoules	Colour rings	Colour ring code is exclusive for each product and dosage form, so that it can be identified before its labelling.
		Secondary Packaging Material	Correct Printing	Correct printing of label, leaflet and carton box is essential to the identification of the product.
	Process	Labelling	Label	The correctness of the label is assured by the correctness of the barcode presented in the label.
			Barcode	
			Colour Ring Quantity and Quality	Colour ring presence and colour is verified in the labelling machine. This also assures the correct Label/Colour ring match in order to correctly identify the product.

CQA	Branch	Step	CQA/CPP	Comments
			Batch and Expiry date printing	The correctness of the printing will assure the correct traceability of the batch and its correct identification.
		Packaging	Carton Box	The correctness of the box and leaflet is assured by the correctness of the barcodes presented.
			Leaflet	
			Batch and Expiry date printing	The correctness of the printing will assure the correct traceability of the batch and its correct identification.

Table 8 - CQAs and CPPs correct identification of product and batch number

3.3. Process Analysis - SVP

There were 65 batches from product X produced during the last year.
This product formulation incorporates besides the API, Sodium Hidroxide and Sodium Chloride. This product is processed through final sterilization and is packaged in amber ampoules.

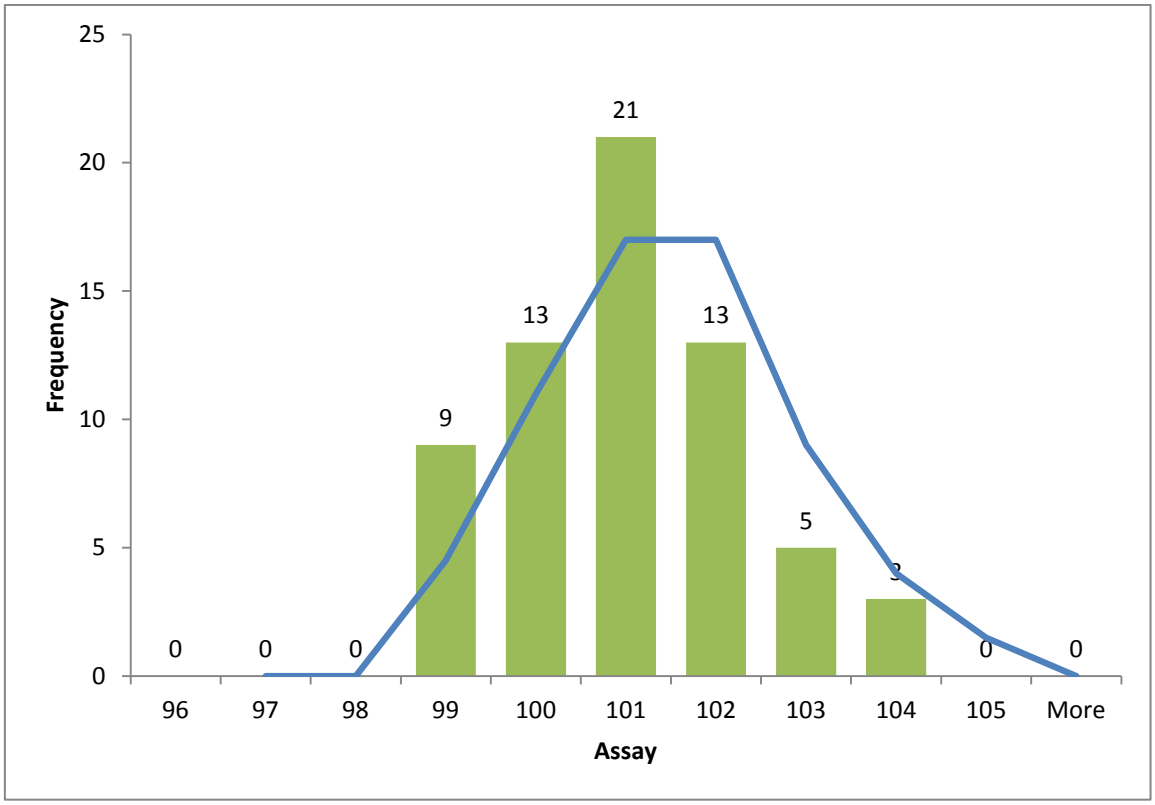
3.3.1. Assay

The Assay was determined for each one of these batches. Specification limits for this parameter are: 95-105%. The obtained results were:

Batch	Assay	Batch	Assay
F001	98,6	F034	100,7
F002	99,4	F035	100,7
F003	100,2	F036	102,4
F004	99,9	F037	101,2
F005	99,3	F038	100,6
F006	101	F039	100,2
F007	100,4	F040	102,6
F008	101,6	F041	102,3
F009	100,8	F042	101,6
F010	100,6	F043	102,5
F011	101,2	F044	102,9
F012	101,8	F045	103,8
F013	101,3	F046	103,2
F014	101,2	F047	100
F015	100,9	F048	101,9
F016	101	F049	101
F017	101,2	F050	99,7
F018	101	F051	100,1
F019	100,4	F052	101,5
F020	100,4	F053	100
F021	99,8	F054	100,5
F022	100,2	F055	99,5
F023	99,2	F056	98,7
F024	103,4	F057	100,3
F025	100,4	F058	99,1
F026	101,3	F059	98,1
F027	101,5	F060	98,1
F028	101,3	F061	98,3
F029	99,9	F062	98,9
F030	98,2	F063	98,4
F031	98,7	F064	99,7
F032	99	F065	99,8
F033	100,7		

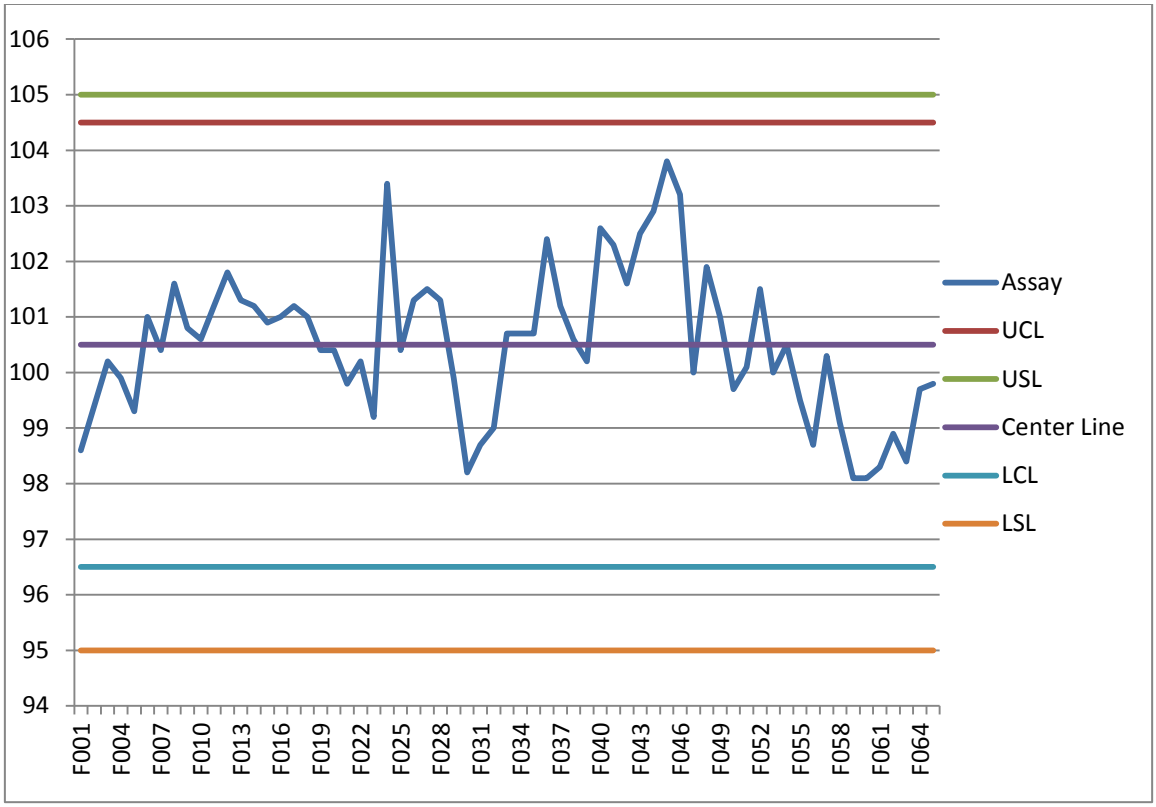
Table 9 – Assay determination values per batch

The histogram for this data is:



Graphic 1 – Assay Histogram

The Control Chart is:



Graphic 2 – Assay Control Chart

From the graphics analysis it is noticed that the process follow a normal distribution, centred around 101%. The control chart reveals that there is an oscillation between 98% and 104%, being all the results within the expected control limits for the process. There were no defective batches manufactured during this period.

Capability indexes were calculated, being Cp 1,25 and Cpk 1,12. These values mean that the Process is capable of producing quality products, being near 4 sigma level.

3.3.2. Impurities

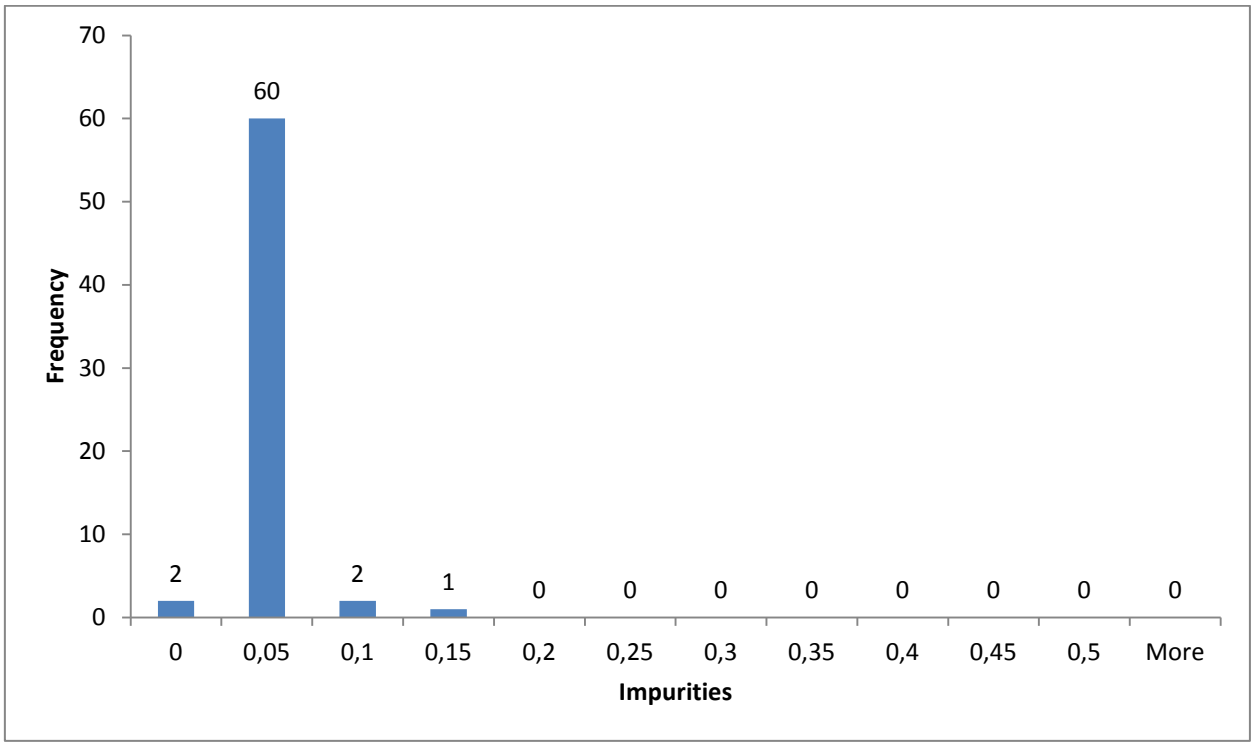
The Impurities were determined for each one of the batches. Specification limit for this parameter is NMT 0,5%. The results were:

Batch	Impurities	Batch	Impurities
F001	0,03	F023	0,03
F002	0,05	F024	0,04
F003	0,06	F025	0,04
F004	0,04	F026	0,04
F005	0,05	F027	0,04
F006	0,03	F028	0,04
F007	0,03	F029	0,03
F008	0,04	F030	0
F009	0,05	F031	0
F010	0,03	F032	0,03
F011	0,03	F033	0,03
F012	0,03	F034	0,03
F013	0,03	F035	0,03
F014	0,03	F036	0,04
F015	0,03	F037	0,04
F016	0,03	F038	0,04
F017	0,03	F039	0,08
F018	0,03	F040	0,12
F019	0,03	F041	0,03
F020	0,03	F042	0,03
F021	0,03	F043	0,03
F022	0,03	F044	0,03

Batch	Impurities
F045	0,03
F046	0,03
F047	0,03
F048	0,03
F049	0,03
F050	0,03
F051	0,03
F052	0,03
F053	0,03
F054	0,03
F055	0,03
F056	0,03
F057	0,03
F058	0,03
F059	0,03
F060	0,03
F061	0,03
F062	0,04
F063	0,03
F064	0,03
F065	0,03

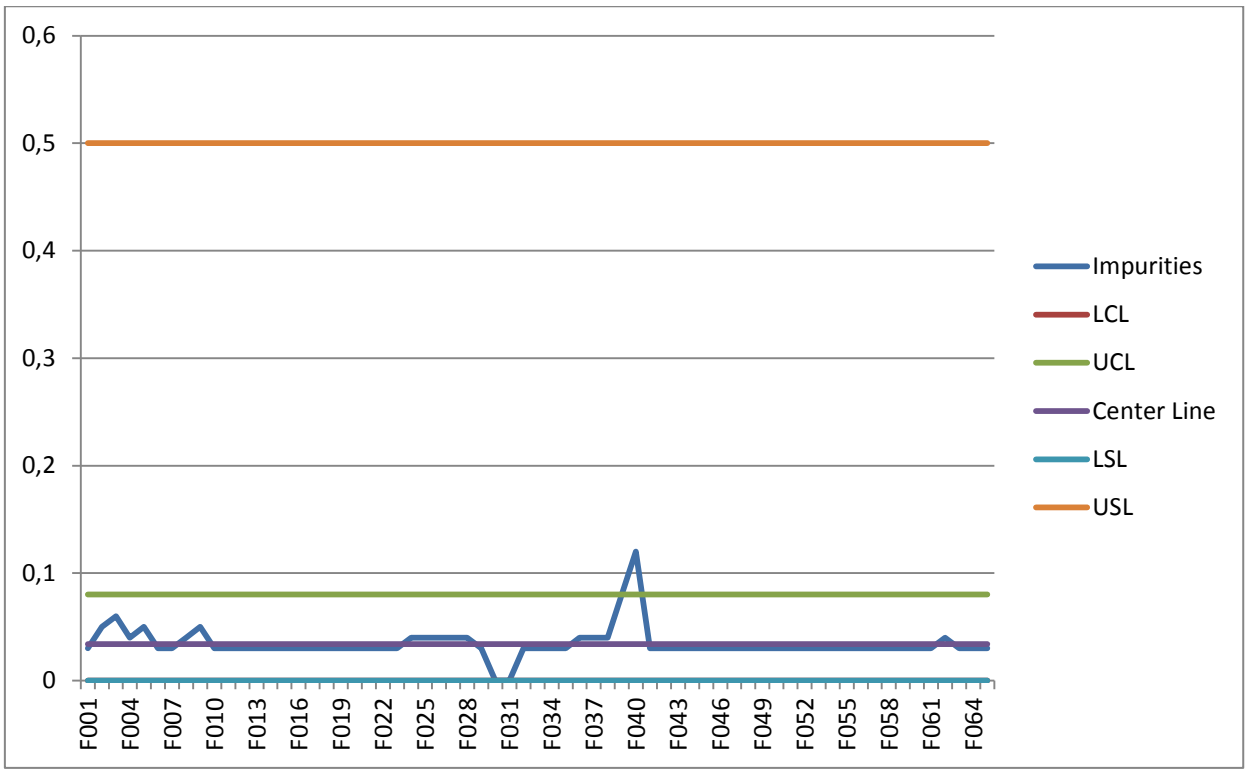
Table 10 – Impurities determination values per batch

The data was aggregated in the following Histogram:



Graphic 3 – Impurities Histogram

And in the following Control Chart:



Graphic 4 – Impurities Control Chart

From the graphics analysis it is noticed that the process follow a normal distribution, centered around 0,05%. The control chart reveals that there is an oscillation between 0% and 0,12%, being all the results except one within the expected control limits for the process. There were no defective batches manufactured during this period, although one value is higher than the UCL. This suggests that this batch was affected by other source of variation, a special cause variation, which should have been investigated.

Capability indexes were calculated, being Cp 5,56 and Cpk 10,35. These values mean that the Process is capable of producing quality products, being higher that 6 sigma level.

3.3.3. Sterility

Regarding Sterility, these batches have been tested according to the EP, being found as sterile, as shown in the following table:

Batch	Sterility
F001	Sterile
F002	Sterile
F003	Sterile

Batch	Sterility
F004	Sterile
F005	Sterile
F006	Sterile

Batch	Sterility
F007	Sterile
F008	Sterile
F009	Sterile
F010	Sterile
F011	Sterile
F012	Sterile
F013	Sterile
F014	Sterile
F015	Sterile
F016	Sterile
F017	Sterile
F018	Sterile
F019	Sterile
F020	Sterile
F021	Sterile
F022	Sterile
F023	Sterile
F024	Sterile
F025	Sterile
F026	Sterile
F027	Sterile
F028	Sterile
F029	Sterile
F030	Sterile
F031	Sterile
F032	Sterile
F033	Sterile
F034	Sterile
F035	Sterile
F036	Sterile
F037	Sterile
F038	Sterile
F039	Sterile
F040	Sterile
F041	Sterile
F042	Sterile
F043	Sterile
F044	Sterile
F045	Sterile
F046	Sterile
F047	Sterile
F048	Sterile
F049	Sterile
F050	Sterile
F051	Sterile
F052	Sterile
F053	Sterile
F054	Sterile
F055	Sterile
F056	Sterile
F057	Sterile
F058	Sterile
F059	Sterile
F060	Sterile
F061	Sterile
F062	Sterile
F063	Sterile
F064	Sterile
F065	Sterile

Table 11 – Sterility determination per batch

The data for sterility reveals that the process is stable and is capable of consistently delivering quality products compliant with the specification.

3.3.4. Endotoxins

Regarding Endotoxins, these batches have been tested according to the EP (kinetic chromogenic method), being all the batches below the detection limit for the equipment, as shown in the following table:

Batch	Endotoxins (IU/ml)	Batch	Endotoxins (IU/ml)
F001	<0,10	F028	<0,10
F002	<0,10	F029	<0,10
F003	<0,10	F030	<0,10
F004	<0,10	F031	<0,10
F005	<0,10	F032	<0,10
F006	<0,10	F033	<0,10
F007	<0,10	F034	<0,10
F008	<0,10	F035	<0,10
F009	<0,10	F036	<0,10
F010	<0,10	F037	<0,10
F011	<0,10	F038	<0,10
F012	<0,10	F039	<0,10
F013	<0,10	F040	<0,10
F014	<0,10	F041	<0,10
F015	<0,10	F042	<0,10
F016	<0,10	F043	<0,10
F017	<0,10	F044	<0,10
F018	<0,10	F045	<0,10
F019	<0,10	F046	<0,10
F020	<0,10	F047	<0,10
F021	<0,10	F048	<0,10
F022	<0,10	F049	<0,10
F023	<0,10	F050	<0,10
F024	<0,10	F051	<0,10
F025	<0,10	F052	<0,10
F026	<0,10	F053	<0,10
F027	<0,10	F054	<0,10

Batch	Endotoxins (IU/ml)
F055	<0,10
F056	<0,10
F057	<0,10
F058	<0,10
F059	<0,10
F060	<0,10
F061	<0,10
F062	<0,10
F063	<0,10
F064	<0,10
F065	<0,10

Table 12 – Endotoxins determination values per batch

The specification for this parameter is ≤35 IU/ml. The data for endotoxins testing reveals that the process is stable and is capable of consistently delivering quality products compliant with the specification.

3.3.5. Particulate Contamination

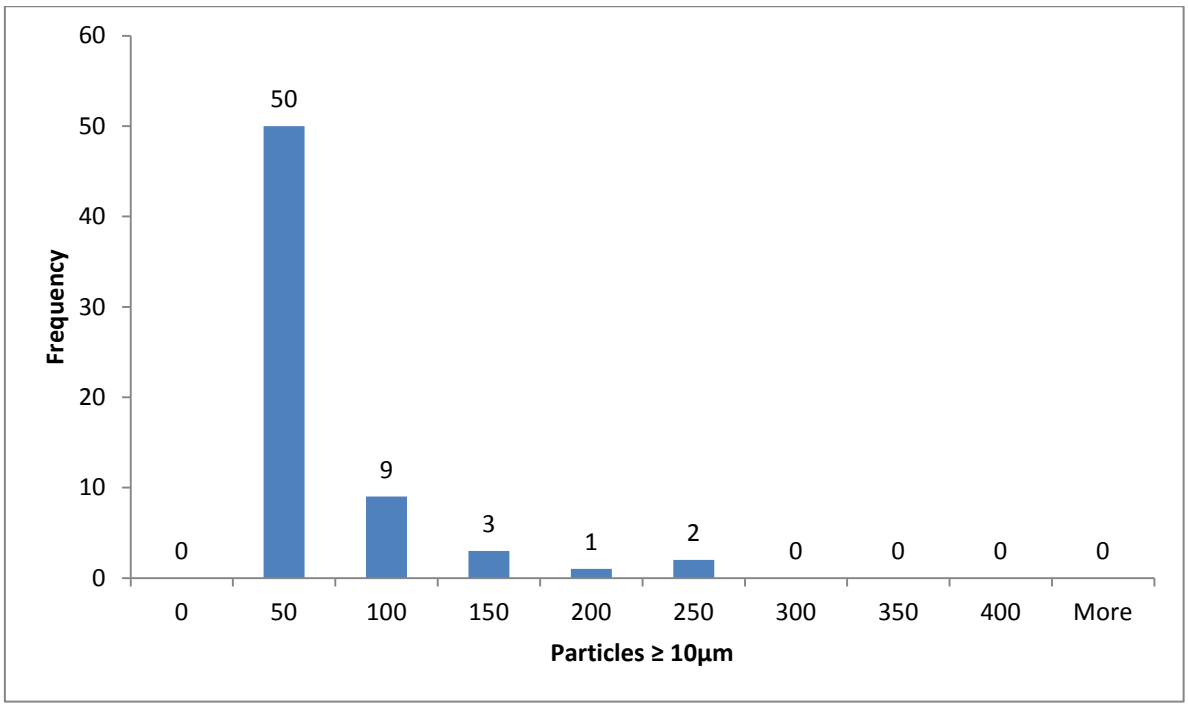
Regarding Particulate contamination, these batches have been tested according to the EP for ≥10µm and ≥25µm particles, being all the batches compliant with the specification, respectively ≤6000 and ≤600 particles per ampoule. The results for ≥10µm particles test are shown in the following table:

Batch	Particles
F001	50
F002	71
F003	21
F004	10
F005	13
F006	16
F007	10
F008	26
F009	27
F010	15
F011	8
F012	60
F013	48
F014	86
F015	233
F016	142
F017	213
F018	19
F019	28
F020	31
F021	21
F022	35
F023	44
F024	14
F025	9
F026	36

Batch	Particles
F027	22
F028	20
F029	28
F030	14
F031	6
F032	4
F033	3
F034	18
F035	31
F036	14
F037	6
F038	7
F039	7
F040	25
F041	7
F042	7
F043	15
F044	12
F045	7
F046	8
F047	55
F048	31
F049	5
F050	27
F051	9
F052	9
F053	56
F054	47
F055	63
F056	84
F057	143
F058	100
F059	32
F060	24
F061	131
F062	170
F063	22
F064	39
F065	55

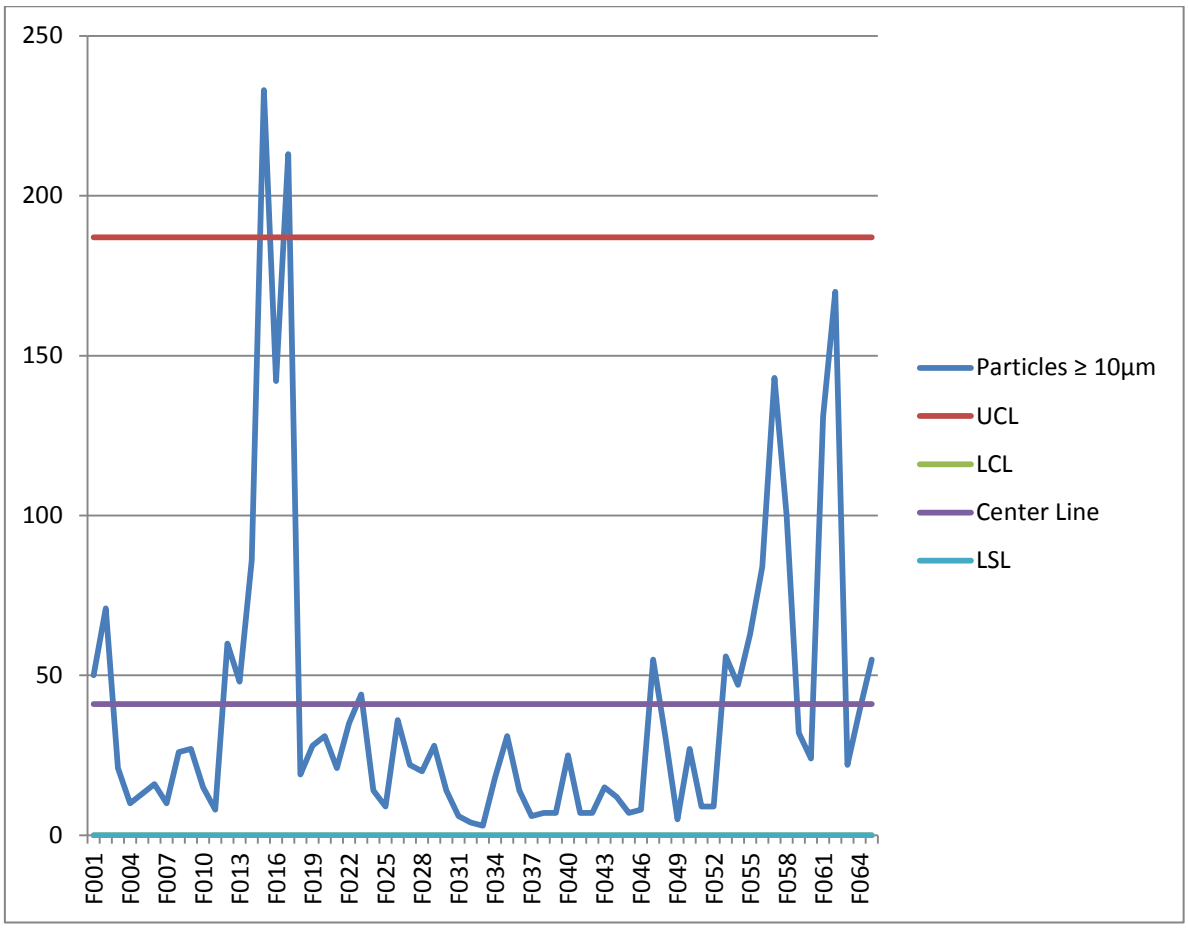
Table 13 – Particulate Contamination (≥ 10µm) determination values per batch

The data was aggregated in the following Histogram:



Graphic 5 - Particulate Contamination (≥ 10µm) Histogram

And in the following Control Chart:



Graphic 6 - Particulate Contamination (≥ 10µm) Control Chart

From the graphics analysis it is noticed that the process follow a normal distribution, skewed to the left, centred around 50 particles/ampoule. The control chart reveals that there is an oscillation being the maximum value observed of 233 particles/ampoule. All results found were within the expected control limits for the process, except two batches. These results suggest that these two batches were affected by other source of variation, a special cause variation, which should have been investigated. Nevertheless, there were no defective batches manufactured during this period.

Capability indexes were calculated, being Cp 20,5 and Cpk 40,8. These extremely high values mean that the Process is capable of producing quality products, being higher than 6 sigma level.

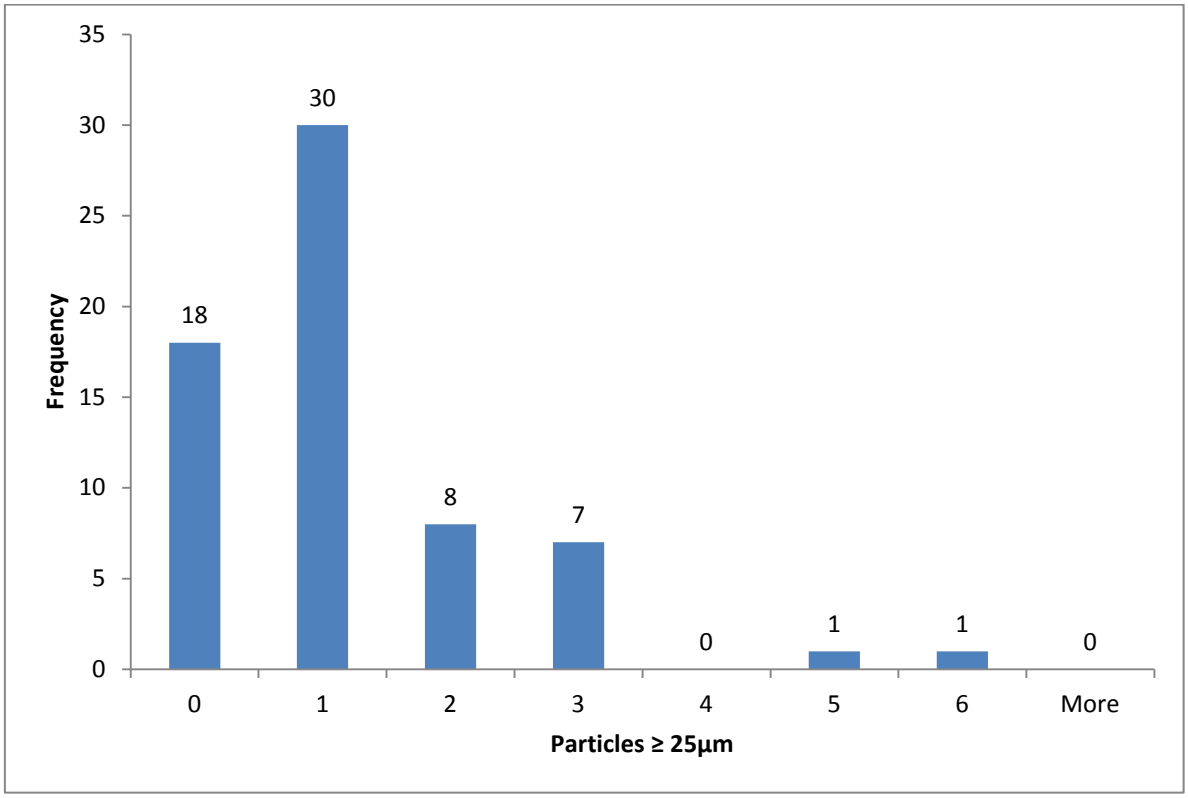
The results for ≥25µm particles test are shown in the following table:

Batch	Particles ≥ 25µm	Batch	Particles ≥ 25µm
F001	1	F020	1
F002	0	F021	1
F003	2	F022	1
F004	1	F023	3
F005	1	F024	0
F006	1	F025	0
F007	0	F026	1
F008	0	F027	1
F009	2	F028	1
F010	1	F029	1
F011	0	F030	1
F012	0	F031	1
F013	1	F032	0
F014	1	F033	0
F015	2	F034	1
F016	2	F035	3
F017	1	F036	0
F018	1	F037	0
F019	1	F038	1

Batch	Particles ≥ 25µm
F039	1
F040	1
F041	0
F042	0
F043	1
F044	0
F045	0
F046	0
F047	1
F048	0
F049	1
F050	2
F051	1
F052	0
F053	2
F054	3
F055	5
F056	3
F057	6
F058	3
F059	2
F060	1
F061	3
F062	3
F063	1
F064	1
F065	2

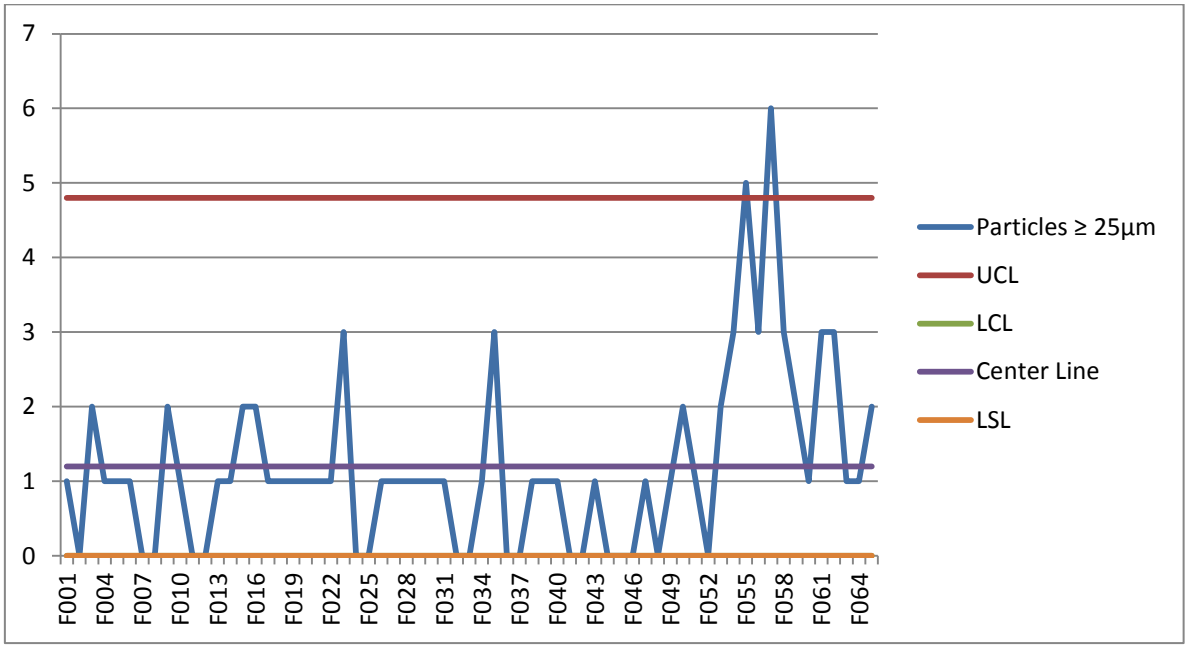
Table 14 - Particulate Contamination (≥ 25µm) determination values per batch

The data was aggregated in the following Histogram:



Graphic 7 - Particulate Contamination (≥ 25µm) Histogram

And in the following Control Chart:



Graphic 8 - Particulate Contamination (≥ 25µm) Control chart

From the graphics analysis it is noticed that the process follow a normal distribution, skewed to the left, centred around 1 particle/ampoule. The control chart reveals that there is an oscillation being the maximum value observed of 6 particles/ampoule. All results found were within the expected control limits for the process, except two batches. These results suggest that these two batches were affected by other source of variation, a special cause variation, which should have been investigated. Nevertheless, there were no defective batches manufactured during this period.

Capability indexes were calculated, being Cp 83,2 and Cpk 166,1. These extremely high values mean that the Process is capable of producing quality products, being higher than 6 sigma level.

3.3.6. Correct identification of product and batch number

Regarding correct identification of product and batch number, these batches have been verified and found to be compliant, as shown in the following table:

Batch	Correct Identification
F001	Compliant
F002	Compliant
F003	Compliant
F004	Compliant
F005	Compliant
F006	Compliant
F007	Compliant
F008	Compliant
F009	Compliant
F010	Compliant
F011	Compliant
F012	Compliant
F013	Compliant
F014	Compliant
F015	Compliant
F016	Compliant
F017	Compliant
F018	Compliant
F019	Compliant
F020	Compliant
F021	Compliant
F022	Compliant
F023	Compliant
F024	Compliant
F025	Compliant
F026	Compliant

Batch	Correct Identification
F027	Compliant
F028	Compliant
F029	Compliant
F030	Compliant
F031	Compliant
F032	Compliant
F033	Compliant
F034	Compliant
F035	Compliant
F036	Compliant
F037	Compliant
F038	Compliant
F039	Compliant
F040	Compliant
F041	Compliant
F042	Compliant
F043	Compliant
F044	Compliant
F045	Compliant
F046	Compliant
F047	Compliant
F048	Compliant
F049	Compliant
F050	Compliant
F051	Compliant
F052	Compliant

Batch	Correct Identification
F053	Compliant
F054	Compliant
F055	Compliant
F056	Compliant
F057	Compliant
F058	Compliant
F059	Compliant
F060	Compliant
F061	Compliant
F062	Compliant
F063	Compliant
F064	Compliant
F065	Compliant

Table 15 – Correct identification of product and batch number determination per batch

This data reveals that the process is stable and is capable of consistently delivering quality products correctly identified.

4. Conclusion

Since 2003 Pharmaceutical Industry mindset is changing. Process Validation stopped being a onetime event to become part of a lifecycle approach.

For legacy products, as the development phase was not as extensive as it is today, it is expected that step 3 is implemented. This can be achieved through a risk assessment of the CQAs and CPPs that can influence product quality and, if there are enough data points, SPC can be applied to the process.

In this project, the essential CQAs and CPPs were identified for the manufacturing of ampoules and SPC was applied to product X. It was verified that the process is under control and most parameters reveal a high capability index. The lower capability index was obtained at the Assay analysis, as this parameter possesses a stricter specification allied to a larger degree of variation in the superior part of the specification (from 98,1% to 103,8%). Regarding this parameter, the process can be improved by the installation of a pump that controls better the quantity of water in the reactor, as the weighed API quantity is maintained.

The followed strategy reveals to be a good strategy to analyse the production process of legacy products although as the development phase was not as extensive, the process experience is the main source of information for the definition of CPPs.

5. Bibliography

[1] ICH - ICH Harmonised Tripartite Guideline, Pharmaceutical Quality System Q10. (June 2008). [Accessed on 21 Sept. 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

[2] HELLE, Marjo-Riitta, et all - A Literature Review of Pharmaceutical Process Validation, PHARMACEUTICAL TECHNOLOGY EUROPE, [Acessed on 16 November 2013] Available on Internet: http://www.pharmtech.com/pharmtech/Regulatory+Affairs/A-Literature-Review-of-Pharmaceutical-Process-Vali/ArticleLong/Article/detail/52258

[3] FDA, Guideline on General Principles of Process Validation, 1987, [Acessed on 22 March 2014] Available on Internet: http://www.brcompliance.com/pdf/TechInfo/process_validation.pdf

[4] FDA, Guidance for Industry - Process Validation: General Principles and Practices, 2011, [Acessed on 22 June 2013] Available on Internet: http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf

[5] EU EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines - Chapter 5:Production, [Acessed on 22 June 2013] Available on Internet: http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/cap5en.pdf

[6] EU EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines - Annex 15:Qualification and Validation, [Acessed on 08 March 2014] Available on Internet: http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/v4an15_en.pdf

[7] ABBOUD, Leila; HENSLEY, Scott - New Prescription For Drug Makers: Update the Plants. The Wall Street Journal. (Sept. 3, 2003). [Accessed on 25 April 2014]. Available on Internet: http://online.wsj.com/news/articles/SB10625358403931000

[8] European Compliance Academy – The new FDA/EU Approach to Process Validation Training April 2014

[9] FDA - Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach, Final Report - Fall 2004 (Sept. 2004) [Accessed on 16 November 2013]. Available on Internet: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm

[10] ICH - Quality Implementation Working Group on Q8, Q9 and Q10, Questions & Answers (R4). (Nov. 116, 2010). [Accessed on 04 July. 2013]. Available on Internet:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_Q_A_R4_Step4_Nov.2010.pdf

[11] FDA - Guidance for Industry, PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. (Sept. 2004) [Accessed on 16 November 2013]. Available on Internet: http://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf;

[12] EMA (CHMP/CVMP) - Guideline on process validation for finished products -information and data to be provided in regulatory submissions. EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1. (Feb. 2014). [Accessed on 08 March 2014]. Available on Internet: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162136.pdf

[13] EU EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines - Annex 15:Qualification and Validation Draft, [Acessed on 25 April 2014] Available on Internet: http://ec.europa.eu/health/files/gmp/2014-02_pc_draft_gmp_annex.pdf

[14] EMA, Concept Paper on the Revision of Annex 15 of the GMP Guide, EMA/INS/GMP/705397/2012 (19 November 2012), [Accessed on 08 March 2014]. Available on Internet: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/11/WC500135154.pdf

[15] PharmOut, White Paper FDA Guidance for Industry Update -Process Validation, Version 01, 2011, [Accessed on 14 June 2014]. Available on Internet: http://www.pharmout.net/downloads/white_paper_fda_process_validation_guidance_final.pdf

[16] Mark Mitchell, Determining Criticality—Process Parameters and Quality Attributes Part II: Design of Experiments and Data-Driven Criticality, BioPharm International, Vol.27 Number 1, January 2014, p.32-40

[17] EMA, Concept Paper on the Revision of the Guideline on Process Validation, EMA/CHMP/CVMP/QWP/809114/2009 (25 February 2010), [Accessed on 01 August 2013]. Available on Internet: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500075029.pdf

[18] European Compliance Academy, The new EMA Guideline on Process Validation – A detailed Analysis, March 2014

[19] PharmOut, White Paper EMA Draft Guidance: Process Validation, Version 01, 2013, [Accessed on 29 March 2014]. Available on Internet: http://pharmout.net/downloads/white_paper_ema_draft_process_validation_guidance_r01.pdf

[20] European Compliance Academy, The new Annex 15 Draft – a detailed Analysis, February 2014

[21] PharmOut, White Paper EU GMP Guide-Annex 15 Qualification & Validation draft released, Version 02, 2014, [Accessed on 28 April 2014]. Available on Internet: http://www.pharmout.net/downloads/mkt_wpr229_EU_GMP_Annex_15_Qualification_and_Validation.pdf

[22] T. De Beera, et al, Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes, International Journal of Pharmaceutics 417 (2011) 32– 47;

[23] Gabriele Reich, Near-infrared spectroscopy and imaging: Basic principles and pharmaceutical applications, Advanced Drug Delivery Reviews 57 (2005) 1109– 1143

[24] European Compliance Academy – Statistical Process Control: A key tool for process understanding in the process validation lifecycle Training May 2011

[25] J.F. MacGregor and T. Kourtl, Statistical Process Control of Multivariate Processes, Control Eng. Practice, VoL 3, No. 3, pp. 403-414, 1995

[26] Montgomery, Douglas, Statistical Quality Control, 6th Edition, 2009

[27] Ronald P. Anjard, SPC chart selection process, Microelectron. Reliab., Vol. 35, No. II, pp. 1445 1447, 1995

[28] PQRI, Process Robustness – A PQRI White Paper, The official manazine of ISPE, November/December 2006, Vol.26, No.6

[29] Chien-Wei Wu et al, An overview of theory and practice on process capability indices for quality assurance, Int.Journ of Production Economics Volume 117, Issue 2, February 2009, Pages 338–359

[30] Susan Haigney , QbD in Sterile Manufacturing, Pharmaceutical Technology Europe, Dec.2013 vol 25 no.12 pp 32