UNIVERSIDADE D
COIMBRA

Ana Beatriz Valentim Pereira

GMPS: PRINCIPLES AND PARTICULAR STANDARDS FOR SPECIAL CLASSES OF PRODUCTS

Dissertação no âmbito do Mestrado em Tecnologias do Medicamento orientada pelo Professor Doutor João José Martins Simões de Sousa e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

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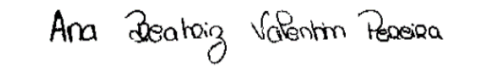

(Ana Beatriz Valentim Pereira)

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Abstract

As previous health incidents showed, health and medicinal products are very sensitive topics, being highly regulated by several agencies. From production to commercialization of a medicinal product, it is found multiple steps to be accomplished. These steps are transposed to processes and need to be regulated, documented, and approved.

To ensure harmonization and regulation, it is imperative to follow the Good Manufacturing Practices (GMPs), guaranteeing compliance through several evaluation methods. Even though the basic requirements of GMPs cover the manufacturing of most medicinal products, there are highly demanding products with very specific inherent characteristics and manufacture such as injectables, hormones and highly potent pharmaceuticals. With this in mind, there are requirements that accompany these product's challenges, thus being relevant to highlight.

And as the practise is as important as theory, once the GMPs are followed and implemented, compliance with the requirements must be demonstrated through a GMP certificate in order to effectively manufacture medicinal products. But how can these particular and challenging requirements affect the access to medicines?

In this line, this thesis will address the historical contextualisation of what led to the present regulation as well as the most relevant agencies for this project. The European GMPs will be covered just as the demanding requirements for the products previously addressed. In a more practical sense, this projects also aims to understand how to prove compliance with GMPs and how can these affect the access to medicines.

Keywords: regulation, GMPs, injectables, hormones, highly potent pharmaceuticals.

Resumo

Como anteriormente demonstrado por incidentes de saúde, a saúde e os produtos de saúde são temas muito sensíveis, sendo altamente regulamentados por várias autoridades. Desde a produção até à comercialização de um medicamento, são encontradas várias etapas por alcançar. Estas etapas são transpostas para processos e necessitam de ser regulamentadas, documentadas e aprovadas.

Para assegurar harmonização e regulamentação, é imperativo seguir as Boas Práticas de Fabrico (BPF), garantindo conformidade através de vários métodos de avaliação. Apesar de os requisitos básicos das BPF abrangerem o fabrico da maioria dos medicamentos, existem produtos altamente exigentes com características de fabrico inerentes muito específicas, como os injetáveis, as hormonas e os produtos farmacêuticos altamente potentes. Neste sentido, existem requisitos que acompanham as exigências destes produtos, sendo por isso imprescindíveis de destaque.

E como a prática é tão importante como a teoria, assim que as BPF são seguidas e implementadas, a conformidade com os requisitos deve ser demonstrada através de um certificado de BPF para que o fabrico de produtos de saúde seja efetivamente possível. Mas como é que estes específicos e exigentes requisitos podem afetar o acesso aos medicamentos?

Nesta linha, esta tese abordará a contextualização histórica do que levou à atual regulamentação, bem como as agências mais relevantes para este projeto. As BPF europeias serão abordadas, tal como os requisitos exigentes para os produtos anteriormente abordados. Numa vertente mais prática, este projeto visa também compreender como como provar a conformidade com as BPF e como estas podem afetar o acesso aos medicamentos.

Palavras-chave: regulamentação, BPF, injetáveis, hormonas, medicamentos altamente potentes.

Outline of the Thesis

1. Introduction

In the first chapter of this dissertation, it is made a contextualisation of the incidents that led to the rise of regulation for medicinal products as well as the inception of regulatory agencies, highlighting and defining the relevant ones for this dissertation and their framework.

2. Good Manufacturing Practices

In the second chapter, the Good Manufacturing Practices are presented with an explanatory approach of its history, its regulatory scope, each chapter requirements and its constituent documents that provide the robustness that characterizes European GMPs.

3. Injectables, Sterile Medicinal Products

Regarding the third chapter, to understand the depth of the GMPs and its importance, injectables and sterile medicinal products are defined and characterized, as well as is made a thoroughly analysis of the Annex 1 of the GMPs that addresses the required and singular manufacturing practices.

4. Highly Potent Pharmaceuticals and Hormonal Medicinal Products

In the fourth chapter, it is addressed the definition of highly potent pharmaceuticals and hormonal medicinal products, just as it is presented the good manufacturing Practices of biological medicinal products in relation to sterile medicinal products, this way highlighting the robustness of EU GMPs.

5. Good Manufacturing Practices Certificate

The fifth chapter is the transition of GMPs from theory to practise, explaining how to obtain a Good Manufacturing Practices Certification to being able to manufacture medicinal products.

6. Pharmaceuticals Economic Assessment

After the understanding of general GMPs and GMPs for more demanding products as injectables, hormones and highly potent pharmaceuticals, the chapter six aims to understand how these meticulous and challenging manufacturing requirements affect the access to medicines.

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Abbreviation List

AIDS – Acquired Immune Deficiency Syndrome

ATMPs – Advanced Therapy Medicinal Products

API – Active Pharmaceutical Ingredient

APS – Aseptic Process Simulation

AS – Active Substance

BFS – Blow Fill Seal

CAPA – Corrective Action, Preventive Action

CCS – Contamination Control Strategy

cGMP – current Good Manufacturing Practise

CTA – Clinical Trial Authorisation

CTD – Common Technical Document

EEA – European Economic Area

EEC – European Economic Community

EFTA – European Free Trade Association

EMA – European Medicines Agency

EMEA – European Agency for the Evaluation of Medicinal Products

EU – European Union

FDA – Food and Drug Administration

FFS – Form-Fill-Seal

FP – Finished Product

GCPs – Good Clinical Practices

GDPs – Good Distribution Practices

GMPs – Good Manufacturing Practices

GPPs – Good Pharmacy Practices

HIV – Human Immunodeficiency Virus

HPAPI – Highly Potent Active Pharmaceutical Ingredient

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

MA – Marketing Authorisation

MAH – Marketing Authorisation Holder

MedDRA – Medical Dictionary for Regulatory Activities

MP – Medicinal Product

NCA – National Competent Authority

NRAs – National Regulatory Authorities

PQR – Product Quality Review

PQS – Pharmaceutical Quality System

PIC – Pharmaceutical Inspection Convention

PIC/S – Pharmaceutical Inspection Convention and Pharmaceutical Co-operation Scheme

QP – Qualified Person

QAS – Quality Assurance System

QMS – Quality Management System

QRM – Quality Risk Management

RABS – Restricted Access Barrier Systems

SAL – Sterility Assurance Level

SiNATS – Sistema Nacional de Avaliação de Tecnologias de Saúde

SOPs – Standard Operating Procedures

SUS – Singles Use System

WHO – World Health Organization

1. Introduction

I. Introduction

1.2. The Rise of Drug Regulation

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." [1]

Therefore, health must be preserved, and diseases must be prevented or in the presence of illness, these must be treated. The prevention and treatment of diseases is made through medicinal products.

The use of medicinal products has been practiced for as long as mankind. However, and unfortunately, regulation isn't as old as medicines. In fact, regulation started as a result of multiple disasters involving medicinal products. These incidents accomplished the realisation of building quality instead of testing quality. [2]

The most known disaster related to the use of poorly tested medicines was regarding the use of Thalidomide, between 1950 and 1960, in Europe. Thalidomide, was a pharmaceutical, fabricated in Germany, initially prescribed as a nonbarbiturate hypnotic sedative that did not induce dependency or hangover. As we know, in the past, drugs were not tested in humans, therefore, Thalidomide did not show any type of toxicity, not being able to detect its lethal dose once it was only tested on rodent models. In the 60s, thalidomide started to being used by pregnant women for morning sickness due to its anti-emetic effect. It was a drug available for everyone, with no prescription necessary and an unexpensive price, therefore, many pregnant women started using Thalidomide, by this becoming a top-selling drug. In the next year, an obstetrician and a paediatrician and geneticist linked the use of Thalidomide with congenital malformations in newborns. In consequence, this medicine was withdrawn from the market. Within a year, 40% of the 10,000 babies affected, died and some pregnancies were not carried until birth. [3]

After being out of the market for almost 40 years, Thalidomide was fully and thoroughly tested and nowadays, is used as a therapeutic agent for Erythema Nodosum Leprosum and for other several dermatologic and inflammatory conditions as well as for cancer. [3]

Other disaster accountable for the beginning of regulation was the Sulfanilamide elixir, even before Thalidomide, occurred in 1937, in which approximately 100 people died from diethylene glycol poisoning. Sulfanilamide was a marketed drug for bacterial infections, in tablet and powder form. The incident occurred when the drug was produced in the liquid form and was not tested for toxicity, being sold as an elixir. As pharmacological studies were not performed, at the time, was not possible to predict that Sulfanilamide dissolved as diethylene glycol, a toxic analogue to an anti-freeze. [4; 5]

This event unleashed the 1938 Act, the basis for United States safety regulations, a subject that was being discussed since the early 1900's. This Act stated that drugs needed safety and efficacy assessment before commercialization, including animal testing, studies that were not undertaken before. [6]

Beyond incidents with pharmaceutical active ingredients, more recently, in September 2022, there was an incident in Gambia with a cough syrup that contained excipients contaminated with diethylene glycol and ethylene glycol, glycols proven to be nephrotoxic for humans. The analysis was performed by FDA, and therefore, on October 5th, WHO issued a health warning concerning four products containing these toxic ingredients, all produced by Maiden Pharmaceuticals Limited (Haryana, India), alerting for it, once it was only detected in Gambia, but may have been distributed to other countries. The ingestion of these products resulted in hundreds of fatalities from acute kidney damaged in children. [7; 8]

Apart from active ingredients and excipients disaster, another event that needed immediate increase in regulation and oversight of medicines was the HIV (Human Immunodeficiency Virus)/ AIDS (Acquired Immune Deficiency Syndrome) epidemic. The origin of HIV-1 goes back to the early 20th century, in West Central Africa. It is believed that this virus originated from a particular strain of Simian Immunodeficiency Virus (SIV), a virus that can be found in chimpanzees by direct contact with chimpanzee blood or meat. Initially, HIV dissipated in local populations in Central Africa for decades before spreading worldwide. Studies show that around 1966, HIV was already in Central America, arriving to the United States of America around 1981. This major time space gave time to the virus go through several mutations leading to the inception of multiple strains and subtypes. The disease started to appear in young homosexual men through rare malignancies and infections. AIDS is transmissible through body fluids such as blood, therefore, in consequence, is passed through sexual contact, parenterally, perinatally and through breastfeeding so, its incidence predominated in intravenous drug users, hemophiliacs and gay men, as stated.

Consequently, it is believed that there was a lack of concern to avoid the virus spread and evolution as well as prevention and treatment due to the affected groups. [9; 10; 11]

Even though there isn't any treatment for AIDS, there are therapies that increase life expectancy and provide a better lifestyle for HIV infected patients. As HIV is a virus, treatment involves antiretrovirals, existing five major classes of pharmaceuticals in use and all of them concern the stages of the viral replication cycle, breaking the cycle, when used combined. The therapies in use are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, integrase inhibitors and entry/fusion inhibitors. [12]

According to the website UNAIDS, at the end of 2021, it is stated that approximately 84.2 million people have been infected with HIV and 40.1 million people have died from AIDS-related illnesses.[13] These statistics make us think about the efforts made to find therapy not only to manage the disease but to eradicate it.

Some decades later, in 2019, the health and pharmaceutical field was put into test with the COVID-19 pandemic. As it is known, COVID-19 was a virus originated in China, derived from bats that killed millions all around the world. The first COVID-19 case was detected in December 2019, in China, arriving to Europe, in Italy, February 2020. At the end of 2020, one year after the disease emergence, at risk groups of people were already being administered with COVID-19 vaccines, developed by several pharmaceutical industries.

After a COVID-19 pandemic, where all efforts were put into practised to understand the disease, prevent spreading and find a vaccine for its prevention, even though HIV epidemic was decades before, it is put into question the work undertaken for it.

Thalidomide and Sulfanilamide were the incidents that showed the need for quality, safety, and efficacy assessment, as well as fuelled the development of regulatory agencies. The HIV and COVID-19 epidemics demonstrated the need for union of all regulatory agencies, to join strengths worldwide to study the viruses, control its spreading and finding a way of preventing it. Thankfully, it was possible to find a way to prevent COVID-19 and the death of thousands of people, unlikely HIV, that unfortunately is still spreading and killing all around the world, remaining only hope that will be developed a vaccine for it in a close future.

At last, it is important to emphasize the latest incident with diethylene glycol and ethylene glycol, proving that even though the pharmaceutical industry is so evolved and controlled, being able to save thousands of lives everyday with medicines, there are countries where things do not work as efficiently, occurring incidents that if not known, it would be predictable that happened in the last century, not in 2022.

1.2. The Inception of Regulatory Agencies

1.2.1. FDA, Food and Drug Administration

The first regulatory agency to appear was FDA, Food and Drug Administration, the regulatory agency of the United States of America, that initiated functions in 1848 in the field of agriculture, evaluating its products for consumption. Later, in 1906 due to the Pure Food and Drugs Act, a law, FDA started to evaluate the commerce of drugs, prohibiting adulterated and misbranded drugs. Due to the Sulfanilamide Elixir incident, in 1938, FDA begun to require and assess the safety of products prior to marketing. [14]

FDA is entitled to the protection of public health in the economic space of the United States of America, guaranteeing safety, efficacy, and security of human and veterinary drugs, as well as Food, Medical Devices, Radiation-Emitting Products, Vaccines, Blood and Biologics, Cosmetics and Tobacco Products. [15]

After the implementation of FDA, numerous countries begun to create its own National Regulatory Agencies (NRAs).

1.2.2. INFARMED, Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

In Portugal, since 1926 the pharmaceutical field was already being assessed, however, started with the inspection of the pharmaceutical practice on its own. Later, in 1945, the evaluation of drugs was put into practise. In 1957, was approved, in Portugal, the first legislation about medicines, in which was stated the need for assessment of drugs quality. In 1986, Portugal joined the European Economic Community (EEC), harmonizing its community directives, which led to the attribution of the "1° Estatuto do Medicamento", the first Drug Statue resulting from the modernisation effort, linking all European directives in only one Legislation. This document covered the marketing authorisation, commercialization, as well as the quality control, safety, and efficacy of medicines. In 1993, the Portuguese National Regulation Authority, INFARMED, was founded. [16]

INFARMED is an NRA, accountability of the Portuguese Health Ministry. The agency is entitled to the insurance of quality, safety and efficacy of medicines and health products. Also evaluates marketing authorisations and monitors the access, commerce, and use of health products, as well as ensures the Good Manufacturing Practices (GMPs), Good Clinical Practices (GCPs), Good Distribution Practices (GDPs) and Good Pharmacy Practices (GPPs) in Portugal. [17]

In addition, INFARMED plays an essential role in the post-marketing authorisation by doing pharmaco-economic studies such as cost-effectiveness for co-funding. This function is designated to SiNATS, the national system for evaluation of health technologies. [17]

1.2.3. EMA, European Medicines Agency

Concomitantly, in the early 1990s, conversations began about the need for a regulatory system for medicines in Europe. Therefore, in 1995 European Medicines Agency (EMA) was created under the name of European Agency for the Evaluation of Medicinal Products (EMEA). [18]

EMA evaluates and supervises medicines in the European Union (EU), eases development and access to medicines, assesses applications for marketing authorisations, monitors safety across medicines lifecycle and provides information to healthcare professionals and patients. EMA has several specialized committees that have key roles in the development and regulation of medicinal products, providing scientific consultancy, preparing guidelines, and contributing to harmonization. [19]

The Agency came into hand in approving marketing authorisations in the European Union, through a single procedure, the centralised procedure, for which evaluation and approval is responsible, along with European Commission. [19]

1.2.4. WHO, World Health Organization

Regarding the World Health Organization (WHO), it was discussed its creation at the time United Nations were formed, in 1945. Therefore, one year later, in 1946, WHO's Constitution came into effect during the International Health Conference, that happened in New York in 1946, being founded on April 7th, in 1948, with the aim to connect nations, people and promote health all around the world. [20]

WHO's is responsible for attaining the highest possible level of health, guaranteeing the well-being of all people, through science, giving equal chances to live for everyone, everywhere, promoting health coverage. WHO also coordinates the response to health emergencies, as well as the prevention and control of diseases. [21]

1.2.5. ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established in 1990 by the regulatory authorities of Europe, Japan, and United States of America. The rise of ICH aimed to meet the need for harmonisation in medicines development and approval. ICH reunites to discuss scientific aspects and technicalities of pharmaceutical products to write guidelines and define standards for the development, registration, and post-approval of medicines. The chosen rules for harmonization are Safety, Quality and Efficacy. [22]

Harmonisation is possible due to the effort of experts by meeting regulatory and industry aspects accomplishing a scientific consensus. Over and above, ICH prevents data overlapping, by preventing duplication of clinical trials, animal testing, between others, and since the standards are the same, thereby, enables that data from clinical trials conducted on one ICH region can be used in other ICH region, just as, the dissipation of information.

ICH also delivered MedDRA, a Medical Dictionary for Regulatory Activities that homogenises medical terminology, it is used for registration, documentation and for the safety assessment, before and after the MA of medicinal products, promoting the use of the same regulatory information. [23]

Regarding marketing authorisation, ICH provides orientation for the Common Technical Document (CTD), this way, reuniting Quality, Safety and Efficacy informations in a harmonised format.

CTD, Common Technical Document

As referred, the CTD is the document, in a standardized format, that reunites and harmonises the information regarding Quality, Safety and Efficacy for the document's regulatory submission. The CTD is divided into five modules, considering that module 1 is region specific and modules 2, 3, 4 and 5 are common for all regions, the information approached by each is the following.

The module 1 is not a part of the CTD since it's regional administrative information, which means, region specific, and thereby regards the Marketing Authorisation, reports, the summary of product characteristics, the information leaflet, and packaging information. [24]

Following, it is the Module 2, which addresses the overall quality summary, a non-clinical overview, a non-clinical summary (pharmacology, pharmacokinetics, and toxicology), a clinical overview and a clinical summary (clinical efficacy and safety, clinical pharmacology studies, biopharmaceutic studies). [24]

Module 3 is focused on Quality, including the active substance and medicinal product chemical, pharmaceutical and biological documentation. [24]

Finally, there is Module 4 and 5, which are the non-clinical study reports and the clinical study reports, respectively. The nonclinical studies assess safety by evaluating the pharmacology, pharmacokinetics, and toxicology of the medicinal product. Efficacy is assessed in module 2 and module 5. [24; 25]

1.2.6. PIC/S, Pharmaceutical Inspection Convention and Pharmaceutical Co-operation Scheme

The Pharmaceutical Inspection Co-operation Scheme was founded in 1995, an extension of the Pharmaceutical Inspection Convention (PIC), in turn, founded in 1970 by the European Free Trade Association (EFTA). In 1970, PIC was founded by 10 countries due to the awareness of the fast development and increased use of drugs, aiming to inspect medicinal product's manufacture. The goal was to harmonise the information regarding inspections as well as its mutual recognition. [26]

Nowadays, PIC/S is incorporated by 54 Participating Authorities, developing common GMP inspection standards with the purpose of harmonising inspection procedures. PIC/S also provides training courses for authorities, more specifically, inspectors, as well as assesses their work. This way, promotes cooperation and communication between authorities, creating a network, just as, develops and manages guidelines and quality systems. [27; 28]

PIC/S mission is "to lead the international development, implementation, and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products. [28]

2. Good Manufacturing Practices

2. Good Manufacturing Practices

Keeping in mind the necessity for control and assessment of drugs quality, safety, and efficacy, just as the importance of guaranteeing that information is equal for all, is essential to establish standards, to harmonise procedures. These along with the rise and relevance of pharmaceutical authorities, Good Manufacturing Practices (GMPs) arise.

Regarding Europe, the first GMPs edition was published in 1989 and already included an annex for sterile products, due to its needed precautions in production. The second edition was published three years later, in the beginning of 1992 which already included 12 annexes. Since then, changes were made, but there was a major re-structuring in 2005, by adding parts according to different specifications, such as Part I is regarding medicinal products for human and veterinary use and Part II refers to active substances used as starting materials. Later, in 2010, Part III was added, corresponding to GMP related Documents.[29] Currently, and since 2017, there is also a Part IV, regarding the GMP requirements for Advanced Therapy Medicinal Products. [30]

GMPs ensure that all products authorized for commercialization in the European market are produced and tested according to the defined quality standards. The goal is to minimize the risks and guarantee quality, safety, and efficacy of pharmaceuticals.

Good Manufacturing Practices are in the EudraLex, "The rules of governing medicinal products in the European Union", Volume 4. This document has an introduction, where is possible to understand the Directives and Regulations for each rule, which are:

- Commission Directive 2003/94/EC of 8 October 2003, laying down the principles and guidelines of good manufacturing practise in respect of medicinal products for human use and investigational medicinal products for human use. [31]
- Regulation (EU) 2019/6 Of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2011/82/EC. [32]
- Commission Delegated Regulation (EU) 2017/1569, of 23 May 2017, supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good practice for investigational medicinal products for human use and arrangements for inspections. [33]

- Commission Directive (EU) 2017/1572, of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use. [34]

The subsequent part of the GMPs is Part I, referring to Basic Requirements for Medicinal Products. Part I is constituted by 9 chapters, being discriminated down as follows.

Chapter 1 – Pharmaceutical Quality System

As already mentioned, the goal of the GMPs is to accomplish quality, efficacy, and safety in medicinal products, however, this result depends on the means, this being the assurance from the Marketing Authorisation Holder (MAH) that the product's manufacture process is in accordance with the respective guidelines. Therefore, for these objectives to be attainable, it is crucial that Good Manufacturing Practices are being followed, as well as Quality Risk and Quality Control are being assessed and that exists Quality Risk Management. With these four components, the Pharmaceutical Quality System (PQS) is implemented.

The definition of PQS is also supported by ICH guideline Q10, where it is found a thoroughly explanation of is scope and management. Also, in the Part III of GMPs, regarding the GMPs related documents, it is possible to find the document "Q10 Note for Guidance on Pharmaceutical Quality System", being this the bridge between GMPs and ICH Q10.

Considering the above, a good PQS must have a consistent manufacturing process, so the product is delivered with the highest quality possible. For this, it important to design, plan, implement and maintain quality.

Quality Management is the outright total of arrangements made to assure that the product has the required quality, managing every matter that influences the quality of the product. Therefore, in accordance with GMPs, quality is built based on several pillars, such as:

- Clearly defined processes, which results in a consistent production, at the product's required quality, this is, compliant with specifications. To maintain a continuous quality, these must be systematically reviewed.
- Procedures and instructions according to MA, Clinical Trial Authorisation (CTA) and/or specifications, as well as followed by qualified and trained personnel, with clearly defined tasks and responsibilities assigned, as well as effective communication between personnel.
- Critical stages and changes to procedures must be validated.
- Fully documentation of everything, enabling records that demonstrate that all steps required were taken in accordance with procedures, resulting in a product with the expected quantity and quality. These records must show the complete history of the batch production, being possible to trace every step.
- Review the product quality in each batch release, enabling the monitoring of the product and processes regularly. After the evaluation of every batch, the Qualified Person (QP) certifies if the batch was manufactured and controlled in compliance with MA, CTA, product specification and/or other regulatory requirements.
- Adequate space, equipment, and materials. Also, it is essential to select appropriate manufacturers/suppliers, as well as monitor their work so it is possible to have the proper starting and packaging materials.
- Intermediate assessment of the product, through in-process controls, monitoring the process performance systems.
- Deviations in the manufacture process must be recorded, investigated to the root cause, and consequently, must be implemented an appropriate preventive action and, if needed, corrective action.
- Beyond the importance of a good production of the bulk product, it is as important to exist a proper labelling, storage, transport, and distribution of the product, in compliance to the Good Distribution Practices (GDP) allowing an adequately shelf-life, as intended.

In addition, on a more specific note, there is Quality Control, the matter of GMPs that concerns sampling, testing, specifications, documentation, organisation, and that states the suitable environment, conditions, and rules in which the medicinal products should be manufactured. Quality Control lays upon some of the aspects above mentioned, as well as furthermore, such as:

- Appropriate facilities and equipment.
- Records of every step, instrument, and testing, showing that all procedures were carried out.
- Sampling and testing of starting materials, packaging materials, intermediate, bulk, and finished products, in adequate environmental conditions, according to GMPs. The finished product shall have the active ingredient quantity and quality composition in alignment with the MA or CTA, at the standard purity. This managing of materials must be handled by trained and approved personnel.
- Product assessment defined by the reviewing and evaluation of relevant production documents.

At last, it's impossible to mention a Pharmaceutical Quality System without referencing the making of a Product Quality Review (PQR). A PQR is the thorough analysis of all collected data from the product manufacture, goaling to assess the consistency of the manufacturing process, the suitability of current specifications for starting materials and finished products, to enhance any verified trends and to detect improvements. These reviews are also relevant not only due to the assessed parameters, but because the previous reviews are considered. PQRs must be annually, however, the periodicity can change. [35]

Chapter 2 – Personnel

Fortunately, the industry is not yet fully automated, therefore, people, more specifically, personnel are still a very important fraction. However, this means that the manufacture of medicinal products relies upon people, being more likely to make mistakes. For this reason, is important to follow rules regarding the hired personnel.

It is important that a company has sufficient trained personnel to carry out all the tasks, as well as individual responsibilities clearly defined, understood, and recorded, however, each one's responsibilities should never be extensive enough to induce any major quality risk. The company must provide training to personnel initially and continuously. Beyond these trainings, workers must have knowledge of the Good Manufacturing Practices that influence their functions directly.

For this to be attainable, the senior management shall provide the appropriate resources, like training, materials, good equipment, and facilities so that is possible to firstly, implement a Quality Management System and then, maintaining it, as well as always seek ways to improve it. The senior management must also establish a quality policy, this being a document that defines the company's point of view and intentions regarding quality. This document must display the willingness to ensure quality in the making of its products, as well as show its suitability to GMPs and consequent effectiveness.

In line with the abovementioned, the company shall provide an organisation chart presenting the relation between key functions and personnel positions, as heads of Production, Quality Control, Quality Assurance and the Qualified Person, which functions should be described in job description. In GMPs, these positions are discriminated and defined due to their relevance and impact on the products quality.

As stated, personnel is a very crucial and critical aspect of each company, being one of the keys to the development of a good quality medicinal product. [36]

Chapter 3 – Premises and Equipment

Premises and equipment must be set up accordingly to their purpose, the manufacturer of medicinal products, therefore, assuring the production's quality.

Along this line of reasoning, GMPs portray several rules to follow regarding the location, design, construction and functioning of premises and equipment.

The general rules include a premises and equipment design and layout that facilitates repair, maintenance and minimises the risk of building-up dirt, as well as an eased and effective cleaning, this according with defined procedures, depending on the products. The environmental conditions such as lightning, humidity and ventilation should also be appropriate and beneficial, not affecting the functioning of equipment as well as product's quality. There shall also exist means to prevent the entry of unauthorised people, mainly in sensitive areas, such as production, storage, and quality control.

Addressing the sensitive areas, each of the abovementioned has strict rules to be followed. Beginning with the production area, this shall, above all, be designed to be protected from cross-contamination, by having a layout in which the production has a logical order of areas corresponding to the sequence of the operation, preventing the risk of misstep. In this line, if possible, there should also exist an area for relevant steps. The surfaces of the areas should facilitate the cleaning and disinfection, as well as must be resistant and prevent the recesses creation.

The storage areas must have high capacity, enough to correspond the needs of orderly storage in the several categories, such as, starting and packaging materials, and intermediate, bulk, and finished products. Additionally, there must also be room for released, rejected, returned, and recalled products as well as products in quarantine. These areas should be dry and clean, with defined special storage conditions, such as temperature and humidity limits, when needed.

Quality control areas are also sensitive due to performed analysis, therefore, shall be separated from production areas, mainly if are biologicals, microbiologicals, and radioisotopes analysis. Mix-ups and cross-contamination should be avoided at all costs.

Regarding ancillary areas, more specifically, rest and refreshment rooms, these should be separated, accessible and adequate to the number of users.[37]

Chapter 4 – Documentation

The traceability of all processes involved in the development, production and control of a medicinal product's is essential to guarantee quality, since this way, it is possible to go back to where mistakes were made and understand how to do better. Over and above, documentation drives the fulfilment of objectives, achieving the envisaged results. Therefore, documentation is a key part of the quality assurance system once establishes, controls, monitors and records every step of the way. However, documentation loses its relevance when it is not monitored as it should be. Accordingly, documents shall be assessed to be reliable, accurate, and legible.

GMPs require certain documents such as the Site Master File, the document that describes the activities developed by the manufacturer and of which more information can be found in Part III, GMP related documents, that will be mentioned further on. Then, documents can be divided into two types of documentation: instructions type or records/report type. Instructions type documents can be:

- Specifications, where the requirements of each material or product are detailed, being used as the key to assess quality.
- Instructions to the manufacturing formulae, processing, packaging, and testing, which provide the information of the materials, equipment, and systems to use as well as the respective instructions.
- Procedures, also known as Standard Operating Procedures (SOPs) describe the directions to perform operations.
- Protocols, provide the instructions to perform and record the operations.
- Technical Agreement, the written contract made for outsourced activities.

On the other hand, the documentation record/report type can be:

- Records, which are the evidence that the instructions were followed, and the actions were performed as expected.
- Certificates of Analysis are the reports of testing results on samples, with the referred stated specification, evaluating the compliance between values.
- Reports, describe the conduct of specific exercises with the respective results, conclusions, and recommendations.

Regarding the generation and control of documentation, it is stated that even though documents can co-exist in hybrid (electronic and paper) or homogenous documentation systems, there are some lines to follow. To begin, control measures for generating documents are essential, such as the pre-existence of master documents, official copies, and the registration of each created document. For electronic documents, the controls may be templates, forms, and master documents. Subsequently, documents with instructions must be approved, signed, and dated by authorised personnel. All documentation shall be unambiguous, uniquely identifiable, reviewed often and kept up to date.

Good Documentation Practices state that records shall be made at the time of the event, and therefore, be traceable. Documents when in paper, must be written in a clear and legible way, and any alteration made to the entry, must allow the reading of the previous information, as well as must be signed and dated.

Trackability of documents also relies upon the retention of relevant information. Regarding production, the batch related documentation is relevant for certain periods of time. Specific documents referring to the batch documentation shall be retained for one year after the expiration of the batch or at least five years after the batch certification from the QP. For investigational pharmaceuticals, these documents must be kept for at least five years after the discontinuation or termination of the clinical trial where the batch was being tested. Critical documents such as raw data, the support for the MA information, should be kept for as long as the authorization is in use. Further documents may need retention, being specificized on the legislation.

Finally, there are some documents that ensure quality of medicinal products and patient safety, whereby, are required, such as specifications for starting and packaging materials, as well as intermediate, bulk, and finished products, manufacturing formula and processing instructions, packaging instructions, batch processing and packaging record, and other procedures and records, such as, the receipt of each delivery, the sampling and testing performed, among others. All these required documents are specified in chapter 4 of EudraLex 4, describing the demanded information to be included. [38]

Chapter 5 – Production

Every GMPs chapter is an important part in building quality, but as can be stated, every mentioned operation is included in the context of production, therefore, as predictable, is the more extensive chapter of the GMPs. Production is the materialization of all instructions and procedures, which must be thoroughly followed.

There are some general guidelines to follow at the production of a medicinal product, such as:

- Actions performed or supervised, when not performed, by competent personnel.
- Correct managing of materials and equipment by trained people.
- Verification, clear and unambiguous labelling/identification, and storage (quarantined if needed) of all incoming materials in the appropriate conditions.
- Protect materials from any type of contamination, and when working with dry materials, avoid dust generation and propagation.
- Follow every rule by the book to prevent deviations, and when occurred, record the deviation, analyse it, and involve Quality Control to approve it.

Being cross-contamination one of the biggest risks in the manufacture of medicinal products, quality risk management measures shall be implemented. Initially, there should be a toxicological and potency evaluation and then, depending on the outcome, technical and organisational measures must be applied. The technical measures can be adjusting the production premises, dedicating one facility if needed (e.g., sterile products), setting the appropriate environment (heating, ventilation, air-conditioning systems, airlocks, pressure cascades) and using adequate material/equipment (disposable, easy cleaning).

Regarding organisational measures, these include the use of appropriate clothing inside high-risk areas, the recording of any accidental event (e.g., spills) or deviations, and planning and designing processes for cleaning that do not present contamination risks, as well as filling of detailed records of the cleaning process, thus ensuring that the cleaning was performed as expected.

When following procedures, some steps, equipment, or materials may need alteration/improvement, therefore, as it may affect quality, when a new manufacturing method is adopted, it needs to be validated and show suitability.

Quality does not depend only on what happens inside the premises, but also what happens outside, before and after production. For this reason, is essential to acquire good quality starting and packaging materials, which can be achieved by tracking supply chains, as well as audit the manufacturers and distributors, assessing if good manufacturing Practices and good distribution practices are being implemented. Additionally, as described in the MA dossier and Annex 8 of GMPs, manufacturers of FP are responsible for testing the quality of starting materials, at least testing a representative sample of each container. Regarding the packaging materials, these must also be sampled and tested, accordingly to different parameters, specified in Annex 8. [39]

Outlining, before any operation, it is imperative to check the cleanliness of materials and equipment, during the operation instructions must be thoroughly followed, every step must be recorded and GMPs shall always be considered and put into practise once it provides specifics for every step of the way. [40]

Chapter 6 – Quality Control

Quality Control is the sector responsible for sampling and testing, assesses the manufactured products quality (finished products), drafts, validates and implements the needed documentation for the correct functioning, assesses the controls made during production, investigates deviations and complaints quality related, and verifies the FP compliance with specifications and GMPs before the release of the product. This must be an independent department, which shall be involved in all quality related decisions.

Quality Control is accountable for the on-going stability programme. This programme is the monitoring of the medicinal product's stability, after marketing, i.e., the assessment of the product's shelf-life, determining if the product remains within specifications.

This is one of the most important departments in each company, having the major responsibility of the product's quality. [41]

Chapter 7 – Outsourced Activities

In the pharmaceutical sector it is common to subcontract other company to perform some activities, these are called outsourced activities, however, being such a regulated industry, is essential to guarantee that the outsourced activity is going to be performed with the same values and requirements as the contractor. Therefore, for these activities, shall be written and signed a contract between the contract giver and the contract acceptor that specifies each responsibility, process, and arrangement. Evidently, this contract shall be written accordingly to the MA and the GMPs.

The contract giver is accountable for the prior assessment of the contract acceptor legality, suitability, and competence to perform the designated task, as well as the delivery of the knowledge needed to carry out the operation, control and review the development of the activities and correspondence to the agreed, and review and assess the records made during operations. The first party must also audit the second party.

On the other hand, the contract acceptor shall be capable of performing the contracted operations, as well as having the adequate material, equipment, premises, knowledge, personnel, and general conditions. The acceptor must not subcontract a third party without the contract giver knowledge and endorsement and shall not make any alteration without the first party awareness and approval. [42]

Chapter 8 – Complaints and Product Recall

The quality of a medicinal product is not only assessed during manufacturing, but also in a later stage, in the market. Even though quality risk is assessed thoroughly on a high-level during production, mistakes are not out of the equation and can be noticed only after the medicinal product's administration.

Therefore, each complaint must be investigated in detail by trained personnel, to the root cause to determinate its extension, and if it is quality related, shall be communicated to the NRA. After the investigation, when results are presented, there should be a decision-making about the measures to be taken, which must have been predicted, and therefore, should be available procedures describing the following steps. In this line, the Corrective and Preventative Actions (CAPAs) are identified and implemented. If the extension of the risk is high, product recall may be possible.

The decision-making process must include, depending on the extension of the defect, the checking of other batches, as well as must consider previous quality defect reports or any registration of problems related to the product.

If the defect affects public or animal health, the batch of the product at issue must be immediately withdrawn from the market, even before the investigation is completed. In case of use in a Clinical Trial, all trial sites must be identified and informed, and the trial must be interrupted as soon as possible. Every step of the way must be recorded until closure and shall be issued a final report.

It is important to understand the seriousness and severity of a defect due to non-compliance of the MA, product specification or GMP requirements. [43]

Chapter 9 – Self-Inspection

As early mentioned, it is crucial to have a good pharmaceutical quality system, therefore, it is important to understand the developed activity and evaluate the need for improvement, this is called a self-inspection. These must scope everything involved in the production of a medicinal product, and therefore, every mentioned fraction of the GMPs abovementioned, must be assessed, such as: the used materials, equipment, premises, the veracity and adequacy of documentation, the production, the performance of quality control and the overall activity. These self-inspections must be frequent and performed by a designated competent person. Everything must be recorded and if need, corrective measures applied.

After addressing the Part I of the GMPs, the following is the Part II, which approaches the Basic Requirements for Active Substances used as Starting Materials. This part of the GMPs was the previous annex 18, and it's the document that guides the manufacture of active substances under a quality system, in compliance to GMPs, guaranteeing quality and purity of the active substances used in medicinal products for both human and veterinary use. This is an extensive document that approaches thoroughly every aspect in the manufacturer of AS, apart from sterile AS that are addressed in Annex 1 of the GMPs, regarding the manufacture of sterile medicinal products. This guideline does not cover active substances that are produced using blood or plasma as raw materials, for these, the manufacture must follow the guidelines in annex 14 of GMPs, as well as does not cover ectoparasiticides. In addition to the use of annex 1, annexes 2 and 7 are also supplementary guidance to the manufacture of active substances, regarding biological active substances and the manufacture of herbal medicinal products, respectively. [44]

Following, in the EudraLex 4, there is the Part III on GMP related documents, which are:

- **Site Master File**, the document that the manufacturer of the medicinal products must prepare and present, regarding the information about the activities carried out in the site, its specific quality management policies in production and the respective quality control. [45]
- **Q9 Quality Risk Management**, guides through the principles and tools for risk management regarding quality, supporting other ICH Quality documents.[46]
- **Q10 Note for Guidance on Pharmaceutical Quality System**, this document regards the ICH Q10 model for a Pharmaceutical Quality System, based on the International Standards Organization (ISO) quality definitions. This guideline intends to improve the quality of medicinal products worldwide by guiding through its development and production. [47]

- **MRA Batch Certificate**, provides information regarding the data to include in the MRA Batch Certification "in the context of mutual recognition agreements, agreements on conformity assessment and acceptance of industrial products" in order to obtain a Batch Certification, certifying that the batch was manufactured accordingly to GMPs and demonstrates quality, safety and efficacy, being this way available for release for sale.[48]
- Template for the "written confirmation" for active substances exported to the European Union for medicinal products for human use.
- Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.
- Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use.
- Template for IMP batch release (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials).
- Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice.
- Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders.

After Part III, is possible to find the 19 annexes of the GMPs, numbered from 1 to 21, since annexes 18 and 20 were discontinued as annexes and were included as the Part II as "Basic Requirements for Active Substances used as Starting Materials" and as a document of Part III, Q9 Quality Risk Management, respectively.

Finally, there is Part IV, the GMP requirements for Advanced Therapy Medicinal Products (ATMPs). This document is very long and extensive due to the specific and complex nature and manufacture of this medicinal products, since ATMPs are biological innovative therapies that use gene therapy, cell therapy and tissue engineering techniques. These therapies are believed to be the future of the pharmaceutical field, and therefore, it is essential to have good regulations regarding its use and production. [30]

3. Injectables

3. Injectables

3.1. Definition and Characterisation

According to the European Pharmacopeia, "injections are sterile solutions, emulsions or suspensions. They are prepared by dissolving, emulsifying, or suspending the active substance(s) and any added excipients in water, in a suitable non-aqueous liquid, that may be non-sterile where justified, or in a mixture of these vehicles." [49]

Regarding the definition of sterility, a product is defined as sterile when has freedom from the presence of viable microorganisms. For a pharmaceutical product, is defined as sterile when the probability of contamination with replicating microorganisms is less than one in a million. [50]

Therefore, the unique production of injections is covered by the Annex 1 of the Good Manufacturing Practices, intitled "Manufacturing of Sterile Medicinal Products".

In this line, just as quality, sterility is not made, it is built, therefore, the manufacture of a sterile medicinal product must be built into sterility, which will be addressed below.

3.2. Good Manufacturing Practices for Sterile Medicinal Products

The scope of this annex is to ensure that the final product (active substance, excipient, primary packaging material or finished dosage form) be microbial, particulate and endotoxin/pyrogen free, or at least prevent its existence. [51]

Non-sterile medicinal products are manufactured in the most clean and contamination free environments, however, in sterile medicinal products, the contamination free must be applied in every step and contamination free strategies must be endorsed.

The addressed chapters of the GMPs are applied to the manufacture of all products, being the annexes composed by additional information. In the case of sterile products, all the above-mentioned shall also be applied, with special attention to sterile conditions, which means that every design, equipment, premises, and personnel must apply the general GMP rules, but considering sterile environments, sterile training for personnel, a stricter control to raw and packaging materials, sterile strategies and processes, between others. [51]

3.2.1. Contamination Control Strategy

For starters, a Contamination Control Strategy (CCS) must be designed and implemented to increase and robust the contamination prevention, once defines the critical control points. Its effectiveness must be assessed, and the measures employed. As any other implemented measures and strategies in the manufacture of medicinal products, the CCS must be reviewed, updated and improved, and consists in the assessment of all GMP factors already identified, such as processes, premises and equipment, personnel, utilities, raw material controls, product containers and closures, vendor approval, management of outsourced activities, process risk management, process validation, cleaning and disinfection, monitoring systems, prevention mechanisms (CAPAs, root cause investigation, trend analysis), continuous improvement, with the addition of preventative maintenance and the validation of sterilisation processes. [51]

3.2.2. Pharmaceutical Quality System

The manufacture of sterile products, mainly requires specific controls, therefore, is important to take this into account during the manufacturing process, such as in the designing of the Pharmaceutical Quality System. Therefore, beyond Chapter 1 of the GMP measures, in sterile production, must be integrated an effective risk management system in all areas of the product lifecycle and applied the risk management in the CCS. [51]

3.2.3. Premises

Regarding the premises, between rooms should exist an airlock functioning as a physical barrier, decreasing the contamination risk. Both doors should not be open at the same time so that the pressure differential is maintained.

Restricted Access Barrier Systems (RABS) or isolators should be included in the CCS, since are barrier technologies that provide protection separating different grade environments according to its level of cleanrooms. There are four grades of cleanroom/zone, A, B, C and D, considering that Grade A is the critical zone for high-risk operations, Grade B is for aseptic preparation and filling and Grades C and D are used for less critical steps.

These cleanroom/zone grades have defined maximum allowed total particle concentration, which are described in the following table, withdrawn from the Annex 1.

Table 1 - Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	At rest	In operation	At rest	In operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

[a] Classification including 5 µm particles may be considered where indicated by the CCS or historical trends.

[b] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

These technologies are different, however, deliver the same function in the critical zone, since both must operate to ensure grade A conditions, by delivering a unidirectional airflow and first air protection. On the other hand, these systems differ in other aspects such as the delivered background environment, the glove system, and the contamination method, all scrutinised in the annex. The choice between both should be based in theses aspects and justified.

It is imperative to qualify and validate the chosen systems, accordingly to Annex 15, regarding "Qualification and Validation" and considering ISO 14644, regarding "Cleanrooms and Associated Controlled Environments". [51]

3.2.4. Utilities, Equipment and Personnel

Regarding utilities, these should be design, constructed, installed, maintained, and assessed in consonance with the needs, preventing microbiological contamination and facilitating disinfection and sterilisation.

Concerning equipment, this is a very relevant part since the equipment can be in direct contact with the product. There are direct and indirect product contact parts, and each must be handled and sterilised correctly.

The personnel must be sufficient, qualified, and trained in accordance with their functions. The behaviour and gowning used should be appropriate to the level of aseptic needs and every cleaning and sterilisation measures to follow must be written and validated. [51]

3.2.5. Production

During the manufacture of products, the level of sterilisation depends on the performed activities since some activities are more susceptible to contamination. Other factors that influence the sterilisation grade of the activity are mainly the type of sterilisation, and therefore, other factors such as, for example, the equipment used, once that if the equipment is slower and the activity takes more time, the contamination risk is higher and therefore, the sterilisation grade must improve. In this chapter, it will be approached the types of sterilisation in products, starting by stating that sterile products can be terminally sterilised or can have a aseptic preparation and processing.

The sterilisation process chosen as being the best is **Terminal Sterilisation**, this means that the products are sterilised in their final container. In this case, usually, the preparation of components and materials is performed in a grade D cleanroom, however, if there is a high risk for contamination, the activity must be performed in C grade. This grade applies also to ointments, creams, suspensions, and emulsions, therefore, filling of products. When the filling is at risk due to a more time-consuming operation, this must be performed at an A grade. The examples of operations and grades for terminally sterilised preparation and processing operations are described in the following Table.

Table 2 - Examples of operations and grades for terminally sterilised preparation and processing operations

Grade A	- Filling of products, when usually at risk.
Grade C	- Preparation of solutions, when usually at risk. - Filling of products.
Grade D	- Preparations of solutions and components for subsequent filling.

When terminal sterilisation is not possible due to several factors such as highly temperature sensitive medicinal products, as it is most of biological medicinal products, tis it should be extensively justified with stability tests as support, and the sterilisation is made through a **filter sterilisation** followed by **aseptic preparation and processing**, which means that every step is performed in an aseptic environment. This technique involves the initial step of filtration through several sterilising grade filter, which retains all viable microorganisms and the following aseptic preparation and processing. The filter must be compatible with the product and accordingly with its MA, and the filtration should be reproduced when possible.

As predictable, being a complex process, this should be described in the CCS as it's controls, which ensure the compliance with the process. In this environment, when feasible, the processes are automated, so it is possible to erase human direct interventions.

The time length for each step must be minimized and limited at a defined duration. In this annex of the GMPs, it is possible to find the following table, Table 3, where is described the process that should be performed in each environmental grade. [52]

Table 3 - Examples of operations and grades for aseptic preparation and processing operations

Grade A	- Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by stem-in-place whenever possible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	- Background support for grade A (when not in an isolator). - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	- Preparation of solutions to be filtered including sampling and dispensing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning. - Assembly of closed and sterilised SUS using intrinsic sterile connection devices.

When is not conceivable to filter the final formulation, all products, components, raw materials, intermediates, and bulk solutions must be sterilised, prior to use.

Terminal sterilisation is the preferred method once it is lethal to microorganisms and is possible to calculate, validate and control the Sterility Assurance Level (SAL).

The terminal sterilisation can be performed through several methods using whether heat, chemical, by radiation or gas.

The heat sterilisation is divided in two methods, moist heat, and dry heat. The moist heat sterilisation is the preferred one and is performed using steam under pressure, this is, in an autoclave, or using other superheated water systems, such as cascades or immersion cycles. In heat sterilisation by dry heat, are used high temperatures of air and gas to remove contaminants more difficult to eliminate. This is performed whether in an oven or in a continuous tunnel process. The sterilisation by dry heat is not very practicable once uses very high temperatures, which degrades the components.

Sterilisation by radiation is performed in heat-labile materials. It is not acceptable to use ultraviolet irradiation, being used ionizing radiation. This is a very effective method, however, is very expensive.

Also, for heat labile products, there is gas sterilisation. Regarding this method, usually it is used ethylene oxide, however, it is a last resourced method, which means that it is applied when no other sterilisation method is possible once spoils most of the components.

The chosen method must be aligned with the material/product specificities, not having a damaging effect, being considered the best method. Usually, the aspects took into consideration is the thermostability and form (liquid, solid) of the material/product.

Other step that highly affects the sterility of the products is the closing of the primary packaging. Ideally, the preparation of terminally sterile products is made through a **Form-Fill-Seal** (FFS) technique or a **Blow-Fill-Seal** (BFS) technique. These methods are for aseptic preparation of the product once the formation of the container, the filling and sealing are steps performed in a machine, in closed sterile chamber. The major difference between both is that BFS technology forms the container from a thermoplastic granulate and FFS technology forms the through a flat roll of packaging film.

When neither of these techniques are possible, every step is performed individually, therefore, there is a major risk of losing stability due to the **holding times**, which can affect the chemical stability by degradation of any component of the formulation, as well as the physical stability by formation of particulates, aggregation, precipitation or separation of phases, and more importantly, the microbiological stability, that is, risking contamination. The holding times refer to the time between two actions. In injectables, these can refer to the holding time:

- Between the cleaning, drying and sterilisation of equipment and components.
- Since the equipment and components sterilisation and actual filling/assembly.
- For a decontaminated environment (RABS or isolator) before use.
- For the sterilised product until filling.
- Pre-filtration time.

The maximum allowed holding time must be defined accordingly with the stability studies of each substance and must be shown that the products approved shelf-life is not affected by the holding times. [51]

Regarding the product's storage, in the needed of prolonging the storage or processing times, all these times should be stated, minimized and consistent with defined limits. The prolonged storage time corresponds to 30 days for solid oral dosage forms and more than 24 hours for sterile products. As stated, the holding time must be supported by stability studies which must be performed under relevant temperature and humidity conditions.

The holding times along the process must be considered in the calculation of the product's shelf life. The shelf life must be calculated accordingly with the "Note for Guidance on the start of shelf life of the finished dosage form".[53]

One way to increase stability is by lyophilization, or freeze-drying, which is a technique that physically-chemically removes the solvents, by sublimation. This is a critical step which must be took into account at the filling step.

Other method that must be considered when mentioning sterilisation is the chosen system to be used, which can be either a closed system or single use system (SUS). In a closed system, the product is not exposed to the surrounding environment until the conclusion of the operation. SUS are, as the name suggests, systems for a singular use. Both options, if correctly manufactured assure continued sterility.

As mentioned, one of the most important strategies to assure sterility is the existence of controls. For that, the site must implement an environmental and process monitoring programme as part of the Contamination Control Strategy, monitoring the controls used along the process. This programme comprises environmental monitoring (total particle), environmental and personnel monitoring (viable particle), temperature, relative humidity and other specific characteristics and Aseptic Process Simulation. [51]

3.2.6. Environmental and Process Monitoring

As mentioned, to assure sterility, which is attainable by preventing microbial and particle contamination, one of the best strategies is the monitoring of the controls through an environmental and process monitoring programme, which is part of the Contamination Control Strategy. This way, it is possible to assure that every product was manufactured under the designed and regulatory environmental conditions as well as deviations from it were detected, on-going risks assessed and subsequently, the products' quality assessed. The environmental monitoring detects the presence of contaminants in the area.

This programme is built based on a risk assessment of the processes, operations, facility, equipment, materials, documentation and critical processes and steps. The risk assessment also helps determine the critical monitoring locations, which are, the locations where the risk of contamination is higher, and therefore, where the controls will be implemented. The selected location of monitoring must be justified, showing appropriateness. This risk assessment must be performed regularly, this way assuring the effectiveness of the programme.

Additionally, alert levels and action limits must be set, which values are described in the GMPs Annex. These alert levels are defined accordingly to the grade of cleanliness (A, B, C or D). Any deviations from action limits must be immediately detected, investigated and preventive or corrective action implemented, existing an operating procedure designed for it. In the case of detection of alert level, this must be assessed, existing an operating procedure for it and for its follow-up.

The monitoring system is composed by four elements, which are:

A. Environmental monitoring – total particle.
B. Environmental and personnel monitoring – viable particle.
C. Temperature, relative humidity, and other specific characteristics.
D. Aseptic process simulation (APS).

Considering only one of these components *per si* does not ensure asepsis. However, when considered together, the outcome of the programme implemented is positive, showing reliability.

3.2.7. Quality Control

As mentioned, the personnel must have appropriate training and experience dealing with sterility assurance and microbiology, as well as knowledge of the processes.

As part of the final batch review, for both terminally sterilised products or aseptically filled products, a bioburden assay must be performed to assess sterility and consequently, safety of the product. Also, this assay should be performed after the sterilisation, whether it is by filter or by terminal sterilisation in order to understand the effectiveness of the method. [51]

Parametric release authorized products, or now called real time release products, which are products that, instead of performing end-product testing, is performed real time release testing, which is the application of a higher control during the process along with the knowledge and understanding of it, which results provide quality assurance. This method that requires authorisation by the competent authority and which is supported by validation of the test method.[54] In this case, a supporting pre-sterilisation bioburden monitoring programme must be developed, and each batch must be tested for bioburden.

However, in the case of end-product testing, obviously, this test is not the only one performed to assure sterility, being only the final test after a process that meet the stated requirements. The sterility test must be taken under aseptic conditions and with a representative sample of the batch, as well as samples taken from parts of the batch that were at a higher risk of contamination, such as for products aseptically filled, samples from the batch at the beginning and ending of the filling, for products terminally sterilised, samples from the worst sterilising locations and samples from lyophilized products, taken at different loads. In the case of existing sub-batches, each must be tested.

In the case of short shelf-life products, sometimes may not be possible to be tested before release, for which situations must exist a strategy or defined methods for additional monitoring and identification of possible risks, which should be assessed and documented.

Additionally, the results of the environmental monitoring programme must be reviewed as part of the batch release/certification.

4. Highly Potent Pharmaceuticals and Hormonal Medicinal Products

4. Highly Potent Pharmaceuticals and Hormonal Medicinal Products

4.1. Definition and Characterisation

Highly Potent Pharmaceuticals are active substances that show a high pharmacological activity at low concentrations. These medicinal products are usually used for the treatment of severe diseases, where it is needed a high and extensive therapeutic effect. It does not exist a guideline for these medicinal products or active substances once can belong to different groups, such as hormones, cytotoxics, between others.

Hormonal Medicinal Products are biological medicinal products that are used to fulfil a hormonal need in hormonal disorders, to balance the hormonal system or even as anti-cancer agents.

Hormonal Medicinal Products are highly sensitive, needing a specialized production unit. Therefore, in the same way as injectables/sterile medicinal products, as abovementioned, supplementary to GMPs Part I and Part II, there is an Annex specifying its production. As they are biological products, the annex of GMPs applied to its manufacture is Annex 2, Manufacture of Biological active substances, and Medicinal Products for Human Use, with the exception of Advanced Therapy Medicinal Products, that originated the Part IV of the GMPs as abovementioned. [55]

Additionally, Annex 2 does not address good manufacturing practices regarding the use of fractioned human blood or plasma and non-transgenic plant products, which are covered by Annex 14 and Annex 7, respectively. Also, is important to note that the use of starting materials such as tissue and cells, and blood or blood components are also covered by additional legislation. [56]

Another particularity of the biological medicinal product's groups is the compulsory centralised procedure for biotechnology derived products. [57]

4.2. GMP Specifications for Biological Medicinal Products

Considering the processes and materials involved in the manufacture of biological medicinal products and its sensitivity and liability, it is possible to comprehend the inherent variability and high contamination risk in this production as well as the necessity of well-defined QRM principles.

The production of biological, deductively, and promptly remits to the cultivation and extraction of cells and other microorganisms from living organisms, therefore, it is put into practise the use of processes that drive the growth of these environments, which can also boost the growth of external microbial contaminants being this one of the major risks of the manufacture of these products. Therefore, the products must be purified in order to minimise contamination events. The purification of biological products is not the same as sterilisation of the products covered by annex I of the GMPs since in a biological environment, there is a level of bioburden, being this very variable accordingly to the managed products, and considering that a sterile product is free from bioburden.

The bioburden is "the level and type of micro-organism present in raw materials, media, biological substances, intermediates or products".

Therefore, some products can be sterilised, and some products can't. These specifications referring if the product must be sterilised or if must have a level of bioburden can and must be found in the Pharmacopeial monographs, MA and CTA.

Likely to steriles, there must be environmental controls, as well as sterilisation and cleaning systems just as the use of closed systems, however, by managing biological materials and products, the controls also involve biological analytical techniques, much more unstable than physico-chemical techniques, therefore, the manufacturing process must be well defined and must present robustness.

Moving on to the guideline itself, this annex is divided into to two parts, Part A and Part B. Part A refers to the guidance on the production, referring to the same topics as other guidelines, this is, addressing the manufacture guideline for each intervenient of the process, such as personnel, premises and equipment, animals, documentation, production, starting and raw materials, operating principles and quality control. Part B refers to the types of biological active substances and medicinal products produced, which will be addressed further ahead.

4.2.1. Part A

Personnel

In the production of biologicals, the main factor taken into consideration regarding personnel, besides the need for specific training, is the health status of the personnel. Employees working in production, maintenance, testing and animal care must be medically monitored regularly and when necessary, vaccinated accordingly with the managed products. For example, personnel working in the production of BCG (Bacillus Calmette–Guérin) vaccine or other tuberculin products must have the immunological status regularly checked or even take x-ray as needed.

Additionally, it is emphasized the need for controlled ins and outs of rooms where there is exposure to live micro-organisms, genetically modified, toxins and animals.

Premises and Equipment

As stated, biological products are very variable and have variability within themselves, therefore, the environment must be adapted to the active substance, intermediate or finished product as well as the manufacture step that is being performed, considering dedicated production areas, for example, to live cells and pathogenic organisms.

Contamination should be prevented instead of remediated, therefore, measures based on the QRM principles must be applied. However, the containment measures must not conflict with product quality measures, and at all times, the equipment and methods used must be designed to prevent any contamination as well as must be periodically tested. Regarding contamination, the principles of sterile production are applied to the manufacture of biological products.

Additionally, to prevent cross-contamination, usually, the manufacture is performed in campaigns, which means that the production of each product is made for a limited period of time with a subsequent cleaning and sterilisation in order to start the production of other product. Nevertheless, even in campaign-based manufacture, must exist an effective control strategy. This control strategy lays upon some principles such as high knowledge of product's and material's key characteristics, study of routes of possible cross-contamination and using single use measures such as closed systems, deep cleaning/sterilisation before and after every manufacture, use of single pass air systems as well as managing of products and equipment.

The manufacture of this type of products must be well planned since biological products, most of the time have a limited lifespan and there is a high risk for total loss of the product.

In addition to the measures addressed in Annex 1, which also apply to biological products, the key characteristics of these products must be considered. For example, in sterile production, as stated, must exist a positive pressure to prevent cross-contamination, but for containment reasons, at the point of exposure of pathogens, must exist a negative pressure and in this case, if the preparation needs to be carried out in an aseptic area, the surrounding environment must be in positive pressure anyways. Similarly to sterile production, these cascades must be clearly defined and monitored by alarm systems.

Systems for sterilisation, cleaning and steaming must be "in place" whenever possible, this is, in the moment and in the same place. Moreover, it is important to manage the air vent filters since these must be hydrophobic.

Animals

In the manufacture of biological medicinal products, as deductible, are used several animal species. The source of animal species can be divided into two groups, the live groups of animals and the materials derived from animals' post-mortem, which are described in Table 4.

Table 4 - Broad types of animal sources for the manufacture of biological medicinal products and its utility.

Sources	Origin	Utility
Live groups	Monkeys	Polio vaccine
	Horses, sheep, goats	Immunosera to snake venoms and tetanus
	Cats	Allergens
	Rabbits, mice, hamsters	Rabies vaccine
	Goats, cattle	Transgenic products
Animal materials post-mortem	Sheep and pigs	Enzymes, anticoagulants and hormones

Beyond being used as sources for materials, animals can also be used as a method of quality control, whether in generic assays such as pyrogenicity or in specific potency assays.

The health of the used animal is also a concern, so there must be an on-going health programme that investigates the source of ill-health occurred instances. For this, must be possible to trace the source, as well as should exist a retained sample from previous collections of the donor animal, that is possible to retest and this way, access its suitability. Beyond an on-going health programme, the prevention and monitoring of infections must be imperative.

As known, animals are very useful in the development and manufacture of medicinal products, but ethics and animals' rights may never be forgotten, therefore, Directive 2010/63/EU must always be considered.

Documentation

If registration of all data and steps is important in the manufacture of any product, then in biological medicinal products, this need potentially increases. Therefore, for starting and raw materials should be documented the source, origin, distribution chain, method of manufacture, and controls applied. In the case of managing human cells or tissue from a donor, is required a full traceability of every substance that was in contact with it since the products arrival until the point of use, maintaining the donor privacy. These records must be kept for until 30 days after the product expiry date.

Production

As mentioned, it is essential to have a robust process to reduce products variability and, as stated, in these products, the variability increases exponentially. Therefore, the process robustness must also increase. In this unique production, the most critical attribute is the cultivation of biologicals for which is intended a cell and microbial organisms' growth, this without forgetting the risk of growing unwanted bioburden. Therefore, procedures and requirements must be well defined and must be thoroughly followed.

Starting and Raw Materials

Every starting and raw material used should be appropriately defined regarding its source, origin, and suitability. All these materials must be compliant with the requirements as well as must be tested before its use.

Considering that the risk and consequences of contamination are equally negative for the finished product, regardless of the time of contamination, the establishment of a control strategy must exist since the beginning of the process. The control strategy for biological starting and raw materials is in consonance with the CCS defined in the Annex 1 of GMPs, previously address. Therefore, quality controls are essential as well as the aseptic manufacturing process, especially when final sterilisation cannot be performed. Regarding sterilisation, when possible, like the sterile products, must be performed by heat.

As abovementioned, the level and type of bioburden defined in the MA or CTA must be seriously considered and respected. When there is a need to reduce the bioburden of materials that were procured from living tissues and cells, this can be carried out using antibiotics, which must be thoroughly justified.

Procurement, donation and testing as well as defined quality and safety of human tissues and cells used as starting materials for the manufacture of biological medicinal products relies upon the Directive 2004/23/EC, which should be thoroughly analysed and considered at the use of these materials.

Seed lot and cell bank system

Seed lots and cell bank systems are a method used to prevent unwanted drift of products' properties at production. Drifting of properties usually happens in products obtained by microbial or cell culture or propagation in embryos and animals due to repeated subcultures/generations.

Therefore, it is important to access the number of subcultures/generations since the seed lot or cell bank until the finished product. This is usually specified in the MA or CTA.

Deductively, the preparation of seed lots/cell banks must be performed in a controlled environment, under the appropriate conditions. Each living material must be handled separately, this means, in an adequate area by the same personnel.

The master and working cell banks and seed lots must be quarantined and release according to the defined procedures, always considering possible contaminants, and therefore, its assessment, by testing. The master and working cell banks and seed lots should demonstrate on-going suitability, as well as consistency in characteristics and quality.

The handling of these materials must be performed adequately by correct identification of the product (seal and label), this way preventing mix-ups. As previously discussed, the materials must be stocked under the defined specifications, at a correct temperature and humidity levels, with the presence of controls.

Regarding the storage of different cells or seeds, this process must be well defined to prevent cross-contamination. However, the splitting of stocks may be preferable, when possible.

Operating Principles

Critical operational parameters and/or processes must be identified, validated, documented, and show compliance with requirements.

Anchored on the quality risk management principles, a control strategy of the entry of materials in production areas must be implemented. Usually, materials enter a clean area through an autoclave or oven, but as mentioned in the previous chapter, regarding steriles, for heat labile materials this method is not possible, therefore, materials should enter the clean area through an airlock.

Regarding culture medias, these include growth promoting properties, which may be demonstrated. Whenever possible, sterilisation of medias should be performed *in situ* as well as the use of sterilizing filters to fermenters through routine addition of gases, media, acids or alkalis, anti-foaming agents.

As abovementioned, contamination must be prevented at all times by carrying out tasks under carefully controlled conditions. For risk production processes, continuous monitoring may be necessary. When contamination occurs, every affected material needs be adequately disinfected and in case of live organism's spillage, this should be managed and dealt with, as safely and as quickly as possible.

At the managing of biological agents, these activities must be performed in a way that prevents contamination or outing of the live agents to the external environment.

Biological medicinal products most of the times are patient specific use, therefore, the printing, storage and labelling must be done carefully and adequately.

Quality Control

For quality control, most measures have already been mentioned throughout the chapter, but a few relevant ones are left to mention. In-process controls is one of them once these ensure consistency of quality through the production. These should be implemented in critical stages important for the finished products' quality.

Regarding sterility tests, these must be performed in antibiotic-free cultures in order to understand clearly and truthfully the absence of bacterial and fungal contamination.

A control strategy for products with a short shelf life must be clearly defined and implemented once batch certification may be needed before the completion of end quality control tests. In these cases, controls need and must be perfectly placed to assess product and process performance, as well as the effectiveness of the quality assurance system must be continuously assessed. Also, alternative tests that demonstrate equivalent data must be considered, such as rapid microbiological methods.

Batch certification is a two-phase method, started by the evaluation of batch processing records, which assess production conditions, possible deviations, and analytical results, and secondly and lastly, the evaluation of final analytical tests by the QP.

4.2.2. Part B, Specific Guidance on Selected Product Types

B1. Animal Sourced Products

Animal Sourced Products are usually obtained from animals in abattoirs, having long and complex supply chains. These supply chains must be documented so that can be traced, as well as must be tested and have controls based on the QRM principles and on the Ph. Eur. monographs requirements.

When using products derived from animals, it is essential to perform a background check, this means, verify the prevalence of animal diseases as well as understanding its origin. In case of sourcing animal products from third countries, the performed standard operations must be assessed and meet the European Union criteria.

To assure the fulfilment of requirements, must exist control measures in the abattoirs from where the animal sourced products are obtained to be used for starting or raw materials. Initially, should exist a quality management system that assures compliance in the operator training, materials traceability, control, and consistency of quality. Secondly, these control measures must also prevent activities that can affect the materials quality, such as the transportation of materials, the purification, and other operating activities.

The abattoirs used as suppliers must also be audited, verifying this way if the controls are being effectively implemented. [56]

B2. Allergen Products

As known, allergy is a disease which does not have a therapeutic cure, only being possible the relieve of symptoms. As allergies are a response of the immune system caused by an interaction of immunoglobulin E antibodies with the allergens, leading to an inflammatory response, the treatment includes a specific immunotherapy with allergen products. [58]

Allergen Products can be extracted from natural sources or can be manufactured through the technology of recombinant DNA, which must be described in detail, such as, the name, origin and nature, contaminant limits and method of collection.

In addition, the process steps and intervenients must also be described in detail just as must be validated. [56]

B3. Animal Immunosera Products

Animal Immunosera Products are sourced from immunised animals and the preparation is made through serum or plasma from these animals. These usually are preparations containing immunoglobulins, especially immunoglobulin G. [59]

Since these products are of complete animal origin, its handling must be performed carefully.

The several steps of the process such as immunisation of the animals, blood or plasma collection, pool-testing, purification, etc, should be performed according to the CTA or MA and the chosen methods of for instance, the purification as well as further modifications must be validated. [56]

B4. Vaccines

According to the "Guideline in clinical evaluation of vaccines", by the Committee for Medicinal Products for Human Use (CHMP), EMA, vaccines are "defined as medicinal products intended for prevention, post-exposure prophylaxis and/or treatment of disease caused by an infectious agent and which contain antigen(s) or genetic information for an antigen(s), either of biological or synthetic nature, that induce a specific immune response against the causative infectious agent(s) or its toxins.".[60]

And according to the European Pharmacopoeia, "vaccines may contain whole micro-organisms that were inactivated, whole live micro-organisms that are avirulent or have their virulence attenuated, antigens extracted or secreted from micro-organisms or produced by genetic engineering or chemical synthesis". [49]

Therefore, when vaccines are produced using human or animal origin, there are some specific rules, addressed in this annex, such as the assessment of a source pathogen-free and which health status needs to be assessed. As referred, the products may have inactivated micro-organisms, which why is necessary to be careful when opening containers with live biological agents.

As vaccines are frequently used to treat high-end diseases with a high biological safety level, which means, with high risk and with the possibility of causing severe disease, deductively, the managing and manufacture of these products must be performed in an appropriate environment, and in higher risk organisms, must exist containment agreements approved by the national authorities. [56]

B5. Recombinant Products

As know, the technology of recombinant DNA is becoming very common and used. According with the European Pharmacopoeia, "products of recombinant DNA technology are produced by genetic modification in which DNA coding for the required product is introduced (…) into suitable micro-organisms such as bacteria and yeast, or a suitable cell line of mammalian, insect, or plant origin. The desired product in the recovered by extraction and purification". [49]

Therefore, being such a specific technology with a unique manufacture, the mentioned steps may be performed in such way to maintain the consistency of the products' quality.[56]

B6. Monoclonal Antibody Products

As European Pharmacopoeia states, "monoclonal antibodies are preparations of an immunoglobulin or a fragment of an immunoglobulin (…) with defined specificity, produced by a single clone of cells."[49]

For this reason, the prevention of infection of infectious agents is imperative. The production cycle must be monitored and compliance with approved limits verified.

B7. Transgenic Animal Products

Transgenic Animal Products are derived from transgenic organisms, for which the definition of transgenic is "an organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials". In this line, there is a predictable inconsistency of the starting materials arising from this technique. Therefore, must be shown consistency of the product batch-to-batch.

The chosen animals must be clearly defined as well as its growing conditions, which means, housing and care so that is possible to predict the exposure of the animals to possible pathogenic agents. As mentioned, in these cases, a health monitoring programme must be considered and implemented, as well as its results assessed.

As a transgenic line usually derives from a single genetic founder, it is important to document its genealogy as well as its managing to prevent mix-ups.

B8. Transgenic Plant Products

In the case of transgenic plant products, the definition is the same as before, however, the source it's a plant instead of an animal.

Similarly to transgenic animal products, the plant that originated the gene must be clearly identified, as well as its health-status assessed since its planting and during its cultivation and harvest, as the existent environmental conditions, such as temperature and rain. More forward, the prevention of cross-contamination as well as contamination by pesticides and fertilisers must be in place, just as the existence of a health monitoring programme.

4.3. Hormonal and Highly Potent Medicinal Products, specialized measures

In the cGMP there are no guidelines regarding the manufacture of hormonal medicinal products and highly potent medicinal products. Hormonal medicinal products are referred in the Annex 2 of the GMPs as biological medicinal products, but further manufacturing methods regarding this group are not addressed. Nevertheless, in the "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities", there is a reference to "certain classes of medicinal product have previously been required to be manufactured in dedicated or segregated self-contained facilities including, "certain antibiotics, certain hormones, certain cytotoxics and certain highly active drug"". And the methods covered by this guideline even though important, do not specify the medicinal products/active pharmaceutical ingredients covered by it, which is relevant once some hormones are highly potent and therefore, more concerning and some are not, for example, insulin is a hormone that can be manufacture in multi-product facilities and other hormones such as steroids can be highly hazard to patients and production workers, being capable of causing adverse reproductive and development effects and "certain hormones" can be so highly potent that equipment can't be fully cleaned, meaning that there will always be product's remaining contaminants meaning that are a hazard to the environment. These risks and worries also apply to other highly potent medicinal products.

Consequently, a quality risk management programme must be developed to assess the hazard of the API and which phases of the medicinal product manufacture and control cycles require specific handling. Even though APIs have threshold limits, a toxicologic evaluation must be performed.

Regarding the quality risk management programme, to protect patient and workers' safety, health-based limits should be implemented such as the acceptable daily exposure (ADE), the permitted daily exposure (PDE), the margin of exposure (MOE), the occupation exposure limit (OEL), the margin of safety (MOS) and the occupational exposure bands (OEBs).

This risk assessment will allow the understanding of the need for segregation, dedicated manufacture, or campaigned manufacture and well as provide protection for workers and patients. [61; 62; 63]

Additionally, WHO developed the "Guideline to the Inspection of Hormone Product Manufacturing Facilities" which defines that "hormone facilities should be classified as containment facilities" and "hormones facilities should be separate, dedicated facilities and should not form part of any other non-hormone facility" which can be a very harsh statement as previously mentioned, some hormones like insulin do not present any hazard.

According to the WHO guideline regarding hormone products, there are eight requirements for which a facility must be reigned by, which are "appropriate facility design and layout", "manufacturing process controls including adherence to standard operating procedures (SOPs)", "environmental control systems (HVAC)", "extraction systems", "personal protective equipment (PPE)", "industrial hygiene", "medical surveillance" and "administrative controls". In addition to the abovementioned, this guideline mentions the need to assess the personal ambient sample (PAS) tests, which indicate the "8-hour time weighted average level of contamination in the operator's breathing zones".

Regarding the personnel protection, the guideline mentions the need for personnel wearing "flashspun, high density polyethylene fibre material suits and shoe/lower leg covers or cleanable boots with integral hoods, as well as single use, disposable later gloves or when in direct contact, double gloves, which must be taped or sealed to the suit, just as wearing a respirator eye and face protection with associated breathing air systems".

The mentioned facility related measures are very similar to the sterile medicinal products facility measures, specifying several important aspects to follow. [63]

5. Good Manufacturing Practise Compliance Certificate

5. Good Manufacturing Practise Compliance Certificate

Following the Good Manufacturing Practices for the manufacturing of standard medicinal products, injectables, in a sterile production and even the assessment of the singularity of hormonal medicinal products and highly potent medicinal products, it is essential to understand how to effectively obtain a certification for manufacturing and this way, being able to manufacture medicinal products.

As known, a marketing authorisation can be submitted by different routes, being this or a European route or a national route. The European route includes three different types of procedures, the centralised procedure, the mutual recognition procedure, and the decentralised procedure.

The centralised procedure is made when the MAH intends that the product(s) is meant to be marketed and available to the European Union with a single marketing authorisation or when the group of the medicinal product belongs to the list of compulsory medicinal products for centralised procedure. This submission is made to the European Medicines Agency, where EMA assesses and evaluates, giving a recommendation to the European Commission, which is the authorising body, granting the authorisation.

The decentralised procedure is the simultaneous authorisation of the medicine in several EU Member States, chosen by the MAH, being possible to submit other decentralised procedures later, if wanted. The mutual-recognition procedure is the authorisation of a medicine in one Member State but its recognition in other EU countries. Even though the MA of centralised procedure is assessed and evaluated by EMA and granted by the European Commission, in the case of the decentralised procedure, there is one member state of reference which national competent authority assesses, evaluates, and grants the MA.

Regarding the mutual recognition procedure, usually is regarding a medicinal product that is already approved in one EU Member State, therefore, since its approval was granted following the European guidelines, its value is “recognized”, being available in the country submitting the mutual recognition procedure.

In the other hand, through the national route, there is the national procedure. Nowadays, the centralised procedure is preferable for innovative medicines and the national route is preferrable for generic medicines or medicines that do not need prescription. The national procedure is the approval of marketing and provision of a medicine in only one Member State, falling within the competence of the national competent authority, the MA assessment, evaluation and further granting, that in the case of Portugal, is INFARMED. [64]

In this line, the manufacturing authorisation depends on the MA, which means that in the case of a MA through a centralised procedure, the compliance with the GMPs will be assessed and manufacturing authorisation will be granted by EMA and in the case of a decentralised, mutual recognition or national procedure, the compliance with the GMPs will be assessed and manufacturing authorisation will be granted by the national competent authority.

Whether is EMA or the National Competent Authority to grant a GMP Certification, the process is the same considering that to obtain a GMP Certification, in the European Economic Area (EEA) is mandatory to show compliance with the GMPs, which is proven through an Inspection to the manufacturing site. In this line, the inspection is performed either by EMA or by the NCA. In the case of having a manufacturing site in a third country, this must also comply with the European GMPs and will also be inspected and in the case of importing from a third country, the importers are responsible for certifying that they comply with GMP. [65]

After the inspection, the GMP Compliance Certificate or the GMP non-compliance statement, will be issued by the NCA in the **EudraGMDP**, which is a database on manufacturing, importing and distribution authorisation as well as GMP and GDP certificates. For mutual recognition agreements with countries outside the EU, these also have access to EudraGMDP. [65; 66]

At the time of the Marketing Authorisation, there is a Pre-Submission where the following informations are requested:

- Name and address of the proposed active substance and final product manufacture(s).
- Name and address of the proposed site(s) in the European Economic Area, for batch release of the medicinal product.

- When imported from a third country, informations of the site and respective inspections from the last 2-3 years performed by EEA competent authorities.
- Final manufacturing and batch release arrangements.
- Description of all involved sites and respective roles.

At this time, inspections will be made to evaluate the site's compliance with GMPs in the 210 day time limit for the evaluation of the application, even for those in third countries, which can delay the MA procedure due to travel restrictions.

After the inspection, when in compliance, GMP compliance certificates will be issued and therefore, importer or manufacturing certificates will be granted, which are necessary for the MA. The inspection is carried out in accordance with the type of production, whether is manufactured a finished product or an active substance.

If the manufacturing site is in the EEA and already registered in EMA's Organisation Management Service (OMS), it is not necessary to perform an inspection for each MA once the inspections are frequently performed by the NCA.

In the case of manufacturing sites in third countries, these will be inspected if the MA is for a different product or a different product's category and if information from the last 2-3 years inspection by the EEA competent authority is not satisfactory.[67]

In EudraGMDP, along with other documents and reports, it is publicly available the issued GMP Compliance Certificates as well as the Non-Compliance Reports, of which an example of each will be given in the Annex of this document, along with the GMP Inspection Report in the Community Format.[66]

6. Pharmaceuticals Economic Assessment based on GMPs

6. Pharmaceuticals Economic Assessment based on GMPs

After the understanding of the manufacturing practices for medicinal products, it is relevant to understand how the manufacturing requirements affect their access. Throughout the analysis of this document, with the enhancing of the manufacturing practices for more demanding medicinal products such as injectables, hormones and highly potent medicines, how can the meticulous handling and rules for these products, affect its access?

The pricing of medicinal products is defined after the granting of the marketing authorisation, and it is at each Member State level. In Portugal the medicine's price is defined by SiNATS which means "system for evaluation of health technologies" and it is based on the principles of reimbursement and that the health technologies price must be assessed during their lifecycle and not only when are granted for a marketing authorisation.

SiNATS is reigned by INFARMED and evaluates health technologies based on a detailed pharmaco-therapeutic and pharmaco-economic evaluation in order to define the fairer prices and understand the technology's acquisition, therefore, is accomplished by the evaluation of pharmaceutical, clinical and economic experts. The goals of SiNATS are:

- Increase the health gains and improve the health quality of citizens.
- Contribute to a sustainable SNS (Serviço Nacional de Saúde), which is the National Health Service.
- Guarantee the efficient use of the health resources.
- Monitor the use and efficacy of the technologies.
- Reduce waste and inefficiency.
- Promote and reward the innovation development.
- Promote the equal access to technologies.

There are several factors that influence the price of the medicines such as the PVP (Preço de Venda ao Púlico) which is the retail price, the added therapeutic value, the cost-effectiveness analysis, the prevalence of the disease at the time and the tool of external price referencing, which is the definition of the pharmaceutical's price based on the prices of other member states. These factors also define the level of reimbursement by the State.

Adding to these factors, the production costs also influence the price of the medicines. For instance, producing a tablet which can be manufactured in a batch of hundreds of tablets, in a regular GMP environment, is not as economic complex as producing injections or hormones, e.g., for single use that are produced in small quantities in order to assure characteristics such as sterility. To note that these must be manufactured in contamination free environments, with more challenging facility layouts and equipment designs, as well as more testing, techniques, and processes. Therefore, is possible to state that good manufacturing prices directly affect the price of medicines.

Conclusion and Future Perspectives

Conclusion and Future Perspectives

The present Dissertation, entitled "GMPs in the view of Injectables, Hormonal and Highly Potent Medicinal Products, as examples" aimed to demonstrate the inception of regulation and which tragedies, incidents and events led to it, as well as the most relevant regulation authorities for the development, manufacture, and marketing of a medicinal product in the European Economic Area.

Following the necessity for control and assessment of the three key characteristics of medicinal products, which are quality, safety and efficacy, just as it is necessary and important to guarantee equal information for all by establishing standards to harmonise procedure, GMPs arise. The Good Manufacturing Practices are supported by a very regulated foundation and principles, being extensive and explanatory, giving this way the secret to an effective, safe and with high quality manufacturing, resulting in the best medicinal products. The full understanding of GMPs is essential, being thoroughly addressed in this project.

Although the general GMPs are quite robust and explanatory, more demanding products with high risks need further requirements. In order to being able to substantiate this statement, in this Dissertation was addressed the unique and challenging characteristics and manufacture requirements of injectables, as sterile medicinal products, and hormones, as biological medicinal products as well as the definition and necessity for regulation of highly potent medicinal products, which at some point, collide with the two first groups. A deeper understanding and regulation of highly potent medicinal products is greatly needed.

GMPs disclose a high deal of specificity and subsequent difficulty in meeting their requirements, which is not easily achievable by all. Therefore, after the deep understanding of the Good Manufacturing Practices for the production of standard medicinal products, injectables, in a sterile production and even the assessment of the singularity of hormonal medicinal products and highly potent medicinal products, it was essential to underlie the importance of following these guidelines and comprehend how to effectively show compliance to it and consequently, obtain a certification for manufacturing, being this way able to produce and market medicinal products.

Even though a deep and extensive regulation brings quality, safety, and efficacy, it was relevant to acknowledge how can these rigorous rules and requirements directly affect the access to medicinal products and how the pricing of a medicine can highly increase due to the manufacturing practices.

This project was made with a Portuguese insight which is covered by European measures and guidelines, for which every citizen should be very thankful. With it, is possible to understand the relevance and importance of regulation and good manufacturing practices in order to guarantee health and good medicinal products with the expected and needed quality, safety and efficacy. However, and unfortunately, these rules and requirements are not practised everywhere and by everyone, being therefore, essential to reflect about the need of knowledge and regulation for all, everywhere, as it was shown by the latest tragedy in Gambia with diethylene glycol and ethylene glycol.

Therefore, this project ends with the statement that there is still a lot of work to be done, a lot of medicines to be regulated and a lot of lives to be saved.

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Annexes

Annex I – GMP Inspection Report – Community Format

Forms Used by Regulators

GMP Inspection Report – Community Format

Table of contents:

Title	GMP Inspection Report - Community Format
Date of adoption	31 January 2010
Date of entry into force	1 August 2010
Supersedes	Version in force from October 2005
Reason for revision	The format was aligned with activities and amendments made in order to enable summary reports for European Medicines Agency inspections to be discontinued

Name of product(s) and pharmaceutical form(s):	*Essential for inspections requested by the European Medicines Agency otherwise only necessary for product specific inspections.*			
Inspected site(s):	*Name and full address of the inspected site, including exact location/designation of the production facilities inspected.* *EudraGMP reference number* *Site location identifier (DUNS number/GPS coordinates)*			
Activities carried out:		*Human*	*Veterinary*	*IMP*
	Manufacture of finished products			
	Sterile	☐	☐	☐
	Non-sterile	☐	☐	☐
	Biologicals	☐	☐	☐
	Sterilisation of excipient, active substance or medicinal product	☐	☐	☐
	Primary packaging	☐	☐	☐
	Secondary packaging	☐	☐	☐
	Quality control testing	☐	☐	☐
	Importing	☐	☐	☐
	Batch certification	☐	☐	☐
	Storage and distribution	☐	☐	☐
	Manufacture of active substance	☐	☐	☐
	Other _____	☐	☐	☐
Inspection date(s):	*Date(s), month, year.*			
Inspector(s) and Expert(s):	*Name(s) of the inspector(s).* *Name(s) of expert / assessor (if applicable).* *Name(s) of the Competent Authority(ies).*			
References:	*Reference number of marketing and / or manufacturing authorisations.* *EMEA reference number(s)if the inspection is requested by the European Medicines Agency.*			
Introduction:	*Short description of the company and the activities of the company.* *<u>For inspections in non-EEA countries,</u> it should be stated whether the Competent Authority of the country, where the inspection took place, was informed of the inspection and whether the Competent Authority took part in the inspection.* *Date of previous inspection.* *Name(s) of inspector(s) involved in previous inspection.* *Major changes since the previous inspection.*			

Brief report of the inspection activities undertaken:	
Scope of Inspection:	*Short description of the inspection (product related, process related inspection and/or general GMP inspection, reference to specific dosage forms where appropriate). The reason for the inspection should be specified (e.g. new marketing application, routine, investigation of product defect)*
Inspected area(s) and main steps/history of the inspection	*Each inspected area should be specified.*
Activities not inspected:	*Where necessary attention should be drawn to areas or activities not subject to inspection on this occasion.*
Personnel met during the inspection:	*The names and titles of key personnel met should be specified (listed in annex).*
Inspectors findings and observations relevant to the inspection; and deficiencies:	*Relevant headings from The Rules Governing Medicinal Products in the European Community, Good Manufacturing Practice for Medicinal Products Vol. IV. This section can link the findings to the deficiencies and be used to explain classification.* *The detail in the narrative of this section of the report may be reduced where a Site Master File acceptable to the reporting authority has been submitted to the Competent Authority.*
Headings to be used New headings may be introduced when relevant	*Overview of inspection findings from last inspection and the corrective action taken.* *Quality Management* *Personnel* *Premises and Equipment* *Documentation* *Production* *Quality Control* *Contract Manufacture and Analysis* *Complaints and Product Recall* *Self Inspection*
Distribution and shipment:	*e.g. Compliance with Good Distribution Practice*
Questions raised relating to the assessment of a marketing application:	*e.g. Pre-authorisation inspections*
Other specific issues identified:	*e.g. Relevant future changes announced by company*
Site Master File:	*Assessment of SMF if any; date of SMF*
Miscellaneous: Samples taken	
Annexes attached:	*List of any annexes attached*

List of deficiencies classified into critical, major and others:	*All deficiencies should be listed and the relevant reference to the EU GMP Guide and other relevant EU Guidelines should be mentioned.* *All deficiencies found should be listed even if corrective action has taken place straight away.* *If the deficiencies are related to the assessment of the marketing application it should be clearly stated.* *The company should be asked to inform the Inspectorate about the proposed time schedule for corrections and on progress.*
Inspectors' comments on the manufacturer's response to the inspection findings:	*i.e. are the responses acceptable?*
Inspectors' comments on the questions/issues raised in the assessment report	
Recommendations for further actions (if any):	*To the Committee requesting the inspection or to the Competent / Enforcement Authority for the site inspected.*
Summary and conclusions:	*The inspector(s) should state whether, within the scope of the inspection, the manufacturer or importer operates in general compliance with the requirements of Directive(s) 2003/94/EC and/or 91/412/EEC, or not, and whether the manufacturer or importer is acceptable for the products in question. (This would apply to situations where there is a degree of non-compliance but where a corrective action plan has been agreed and the inspector has no reason to believe that it will not be implemented and where there is no immediate threat to public health).*
Name(s): **Signatures(s):** **Organisation(s):** **Date:** Distribution of Report:	*The inspection report should be **signed and dated** by all inspector(s)/assessors having participated in the inspection.* *For inspections requested by the European Medicines Agency the inspection report should be forwarded to the Agency.*

Definition of Significant Deficiencies

1 Critical Deficiency:

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2 Major Deficiency:

A non-critical deficiency:

which has produced or may produce a product, which does not comply with its marketing authorisation;

or

which indicates a major deviation from EU Good Manufacturing Practice;

or

(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

or

which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such;

3. Other Deficiency:

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).

Annex 2 – GMP Compliance Certificate

National Authority Of Medicines And Health Products

CERTIFICATE NUMBER: ***F051/S1/ME/003/2023***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 15 of Directive 2001/20/EC

The competent authority of Portugal confirms the following:
The manufacturer: ***Generis Farmaceutica S.A.***

Site address: ***Rua Joao De Deus N 19 Venda Nova, Amadora, 2700-487, Portugal***

OMS Organisation Id. / OMS Location Id.: ***ORG-100002362 / LOC-100000372***

Has been inspected under the national inspection programme in connection with manufacturing

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2023-01-12***, it is considered that it complies with:

- The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and Commission Delegated Regulation (EU) 2017/1569 [3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2.The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

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[1] *The certificate referred to in paragraph Art. 15 of Directive 2001/20/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

1 MANUFACTURING OPERATIONS	
1.2	**Non-sterile products**
	1.2.1. Non-sterile products (processing operations for the following dosage forms) 1.2.1.1. Capsules, hard shell 1.2.1.2. Tablets
1.5	**Packaging**
	1.5.1. Primary Packaging 1.5.1.1 Capsules, hard shell 1.5.1.2 Capsules, soft shell 1.5.1.13 Tablets
1.6	**Quality control testing**
	1.6.1. Microbiological: non-sterility *1.6.1. Chemical/Physical*

2023-03-22

Name and signature of the authorised person of the Competent Authority of Portugal

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Confidential

National Authority Of Medicines And Health Products

Tel:***Confidential***
Fax:***Confidential***

Italian Medicines Agency

Report No: ***IT/NCR/API/02/2022***

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer[1]

Part 1

Issued following an inspection in accordance with:
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of Italy confirms the following:
The manufacturer: ***Bioindustria Laboratorio Italiano Medicinali S.p.A.***

Site address: ***Via De Ambrosis 2-6, Novi Ligure, 15067, Italy***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2022-09-01***, it is considered that **it does not comply with the Good Manufacturing**

Practice requirements referred to in

- The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

[1]*The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

Part 2

1 NON-COMPLIANT MANUFACTURING OPERATIONS	
Include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;	
1.4	**Other products or manufacturing activity**
	1.4.1 Manufacture of 1.4.1.3 Other: active substance(en)

Manufacture of active substance. Names of substances subject to non-compliant:
HYALURONIDASE(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance:HYALURONIDASE	
3.2	**Extraction of Active Substance from Natural Sources**
	3.2.2 Extraction of substance from animal source
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps: lyophilisation 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing 3.6.4 Biological Testing

Part 3

1.Nature of non-compliance:
The Company is manufacturing only the active substance Hyaluronidase, enzyme extracted from bovine testes. Almost all the API manufactured was utilized to produce in house Injectable medicinal products according to Art. 5 (1) of Directive 2001/83/EC. No Registration File/Marketing Authorization was submitted by any MAH. Concerns raised about the following: Risks of cross contamination between pre and post viral inactivation activities due to absence of HVAC systems. Furthermore, same equipment were utilized for both manufacturing steps. Failure to manage the containment during pre- viral inactivating acitivities: some operations were not performed in closed systems. Failure to manage cleaning activities: no contact time of inactivating agent (NaOH 1M) was validated for contact parts equipment. Only one washing room was available to clean equipment used for pre and post inactivation activities, finishing steps and storage of cleaned equipment. Failure to manage bovine testes' supplier validation: supplier was never audited. No risk assessment respect to viral safety was carried out for evaluation of risks related to manufacturing of active substance Hyaluronidase. No analytical testing for determination of eventual adventitious agents were performed on industrial batches but only laboratory testing were available. Suspension of the manufacturing authorisation No. API - 151/2021, issue date 2021/09/21. No Registration File/Marketing Authorization was submitted by any MAH.

Action taken/proposed by the NCA

Withdrawal, of current valid GMP certificate No. IT-API/154/H/2018
Withdrawal of current valid GMP certificate n. IT-API154/H/2018, issue date: 2018-09-05

Recall of batches already released
No active substance Hyaluronidase batches were released on the market for manufacturing medicinal products. Active substance Hyaluronidase was utilized to produce in house Injectable medicinal products according to Art. 5 (1) of Directive 2001/83/EC.

2022-10-07

Name and signature of the authorised person of the Competent Authority of Italy

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