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GOOD MANUFACTURING PRACTICES (GMPs) AND PROCESS VALIDATION IN THE PHARMACEUTICAL INDUSTRY: AN IN DEPTH ANALYSIS

MASTER THESIS OF GERASIMOS VOYKELATOS

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ΠΑΡΑΡΤΗΜΑ Δ : **ΥΠΕΥΘΥΝΗ ΔΗΛΩΣΗ** **ΕΚΠΟΝΗΣΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ**

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GOOD MANUFACTURING PRACTICES (GMPs) AND PROCESS VALIDATION IN THE PHARMACEUTICAL INDUSTRY: AN IN DEPTH ANALYSIS

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Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου.

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Abstract

One of the most important pillars of our modern society is the healthcare system, an integral part of which is the pharmaceutical manufacturing industry. This sector has grown to be one of the most complex, internationalized, and value adding.

This dissertation begins by covering the reasons for choosing this subject and continuous by further justifying this through a thorough industry analysis. It then moves forward to study the history of Good Manufacturing Practices and how they became a necessity to ensure pharmaceutical product quality in today's multipolar world. All major regulatory frameworks are relayed (International Conference on Harmonization, E.M.A., F.D.A., W.H.O., U.K., China, Pharmacopeias, I.S.O., P.I.C./S) and their key similarities and differences are discussed.

The European regulatory framework is chosen for further examination, and this is provided through a chapter-by-chapter analysis of the guidelines for industry, drawn up by the European Medicines Agency. In addition, a list of every supplementary annex is given.

Closing, the thesis examines the subject of validation and its importance as a tool for keeping production under a state of control and establishing proof of repeatability and quality. Finally, different types of validation are examined, focusing on the steps followed, their requirements and the necessary documentation.

Key words: Pharmaceutical Industry, GMPs, EMA, Guidelines, Process Validation

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Section 1. Introduction

The history of medicine is almost as old as mankind. It begins even before the written history. Although it is very hard to interpret the exact way people used to live in that era, findings, such as tools and body remains of early humans, indicate the existence of an early form of medicine. Even though it has its roots in prehistoric times, guidelines that ensure the quality and safety of drugs and medical devices began to be seriously and diligently enforced only in the middle of the 20th century. Unfortunately, it took tragic accidents – that claimed the lives of millions of people – for these guidelines to be established in the industry and incorporated into manufacturing practices and national law.

During the dawn of human civilization, practice of medicine was based on trial and error. Humans distinguished which plant seemed to serve as food, had medicinal value or was poisonous. Of course, all the above, applied only in common infections. More serious maladies believed to be of supernatural origin. Magic and religion played a huge part in prehistoric societies. Dancing, grimaces, incantations, and remedies were a common practice. The first doctors were witch doctors.

During the 3rd millennium BC, Imhotep lived in Egypt. He is believed to be the first physician and later was regarded as the Egyptian god of medicine. In the 19th century, a papyrus was discovered, containing spells, remedies, and basic surgical treatises. In contrary to popular belief, despite having mastered the process of mummification, ancient Egyptians had limited anatomical knowledge.

In India, during 1000 BC and 800 BC, Hindu physicians started employing all five senses to perform diagnosis and they appeared to have a very good clinical sense as a result. At the same time, they focused on dietic treatment and vegetable drugs as well as on more active treatments, known as “The Five Procedures” (administration of emetics, purgatives, water enemas, oil enemas and sneezing powders). Inhalation, leeching, cupping, and bleeding were used too. Also, there are evidence of surgery practice such as excision of tumors, extraction of foreign bodies and punctures to release fluid in the abdomen, using alcohol as a narcotic and hot oil to stop the bleeding.

While most countries influenced one another, Chinese system of medicine remained independent of any kind of external influences until the early 19th century. Even today, native system is widely practiced throughout the country. This system is based on the philosophy of yin and yang. Illnesses are thought to be a result of some kind of unbalance between these two forces. China is also famous for the practice of acupuncture, where thin needles are inserted into the body in order to relieve stress, pain or tension. Hundreds of specific points were mapped through the centuries and today the exercise of this procedure is gaining increasing popularity in the west as an alternative new age approach.

The roots of Western Medicine can be traced back to ancient Greece. Greece has inherited much from Babylonia, Egypt, India, and China but took this knowledge to the next level. Asclepius temples are considered the prototype of modern health resorts where people went to recuperate in a soothing and peaceful environment. Also, it was the early philosophers that led the way to abandon magic and seek reason. Empedocles was the first to advocate the idea that the universe is composed of four elements (fire,

air, earth, and water) and humans of four bodily humors (blood, phlegm, choler and melancholy). As was the case with yin and yang, health according to Empedocles, was a direct result of the harmony between these four.

In 460 BC Hippocrates, who is considered the father of medicine, was born. Little is known about his life and many support the idea that Hippocrates maybe was in fact several men. He paved the way for disease to start being regarded as a natural phenomenon while doctors were encouraged to look for physical causes. Based on these principles, Aristotle became the first great biologist and set the foundation of comparative anatomy and embryology.

Medicine traversed a peculiar path during the Dark ages. Christian Church reemerged the belief that diseases were a divine punishment laid upon the sinners but at the same time monks are to be thanked for the translation and preservation of classical manuscripts. At the same time, in a different geographical place, in Muslim empire, alchemists in pursuit for the philosopher's stone discovered, named, and characterized numerous substances.

Carrying on the scientific stagnation, no major breakthrough was achieved in the course of Middle Ages. Nevertheless, these were the centuries that some of the first major hospitals were founded in Europe, such as the ones in Salerno, Bologna, and Padua (Italy) and in Montpellier and Paris (France).

One of the biggest problems of medicine up to this point was the very limited anatomical knowledge. This was a direct result of human dissection being forbidden because of religious beliefs. Renaissance and the new way of thinking that cultivated, allowed for these prohibitions to be slowly lifted. In consequence, the first ever complete practical manual of anatomy was published in 1316 under the title "Anathomia Corporis Humani" by Mondino de Luzzi.

Scientific progress began to accelerate again during the Enlightenment. New chemistry knowledge was acquired, William Harrey proposed the theory of circulation, which was a milestone in understanding how the human body works and microscope was invented, allowing to see and describe bacteria for the first time.

18th century was a period that marked by the evolution of surgery across UK. Moreover, late in the century stethoscope was discovered giving a boost in physical examination and vaccination began to take place in a systematic manner. It was during this eon that population statistics began to be kept for the first time and suggestions arose concerning health legislation.

From this point onwards, scientific advancement became exponential. During the course of 19th century, physiology blossomed in Germany and France, Germ Theory became verified, and Louis Paster established the science of bacteriology which in turns led to more refined techniques of sterilization and identification of many disease producing microorganisms, such as cholera and tuberculosis. Across the Atlantic, in America, general anesthesia was introduced changing the way surgeons operated for ever.

To complete all the above, Parasitology arose as an independent field that explained how diseases were transmitted, X – Rays were discovered in 1895 by Wilhelm Conrad and Radium in 1898 by Pierre and Marie Curie. Lastly, it was in this time of continuous improvement that Sigmund Freud gave birth to the vast new field of psychiatry.

The 20th century came alongside with big improvements in the field of communication between scientists throughout the world. With communication came progress and with progress more precise diagnostic tests (sonar, Cat, NMR), more effective therapies (sulfonamide drugs) and magnificent advances in biomedical engineering. This century was marked by the discovery of penicillin (first time commercially produced during the World War 2) in 1928 by Alexander Fleming which led to antibiotics.

Moreover, Immunology helped to bring viruses under control by understanding the role of the white blood cells, that is the process of how the human body reacts while fighting infectious organisms. This newly acquired knowledge allowed the production of the first safe and effective antiviral vaccines, such as typhoid vaccination (mainly for British troops serving in the South African war), tetanus, diphtheria, and BCG vaccine for tuberculosis.

In the second half of the century, tissue culture was introduced and offered the means to grow viruses in the laboratory. This, combined with the discovery of the electron microscope, improved even further the quality of vaccines, and had a whole new generation of them as a result.

More major breakthroughs were due to advancements in Endocrinology. The discovery of insulin was a lifesaving moment for people with diabetes, cortisone gave potent anti – inflammatory agents, birth control became possible based on the study of sex hormones, vitamins were identified and categorized, and improvements were made in radiation therapy and chemotherapy for cancer.

Unfortunately, last century was deeply stigmatize by two World Wars. Medicine was affected in numerous ways. The most significant impact was made in the field surgery. World War 1 gave innumerable lessons to surgeons and hand on experience of a lifetime. Then, between the 2 World Wars, this experience blossomed and allowed surgery to consolidate its position. Anesthesia became better, the aseptic method for sterilization was established, rubber gloves and gauze masks started being used during operations and shock mechanism was deeply understanded and blood transfusion was used as a counteraction.

Specialization became more thorough in the fields of abdominal surgery, neurosurgery, and radiology. During World War 2, doctors started serving as special units in the first lines, providing wounded soldiers with first aids in unimaginable conditions. Valuable lessons were taken regarding wound infections and teamwork of specialized surgeons was promoted. After the war, the first open heart surgery took place and organ transplantation became possible for the first time.

The 21st century seems to have decided to focus on collaboration between medicine and new technologies as a way forward. In an interconnected world, more and more people turn to telehealth services to receive healthcare advice or a first diagnosis. New methods of drug development and nanomedicine allow for more effective and precise medicines,

or even personalized drugs for every individual patient. 3D printing method is used to create implants, joints, or even artificial organs in the lab. Also, more and more commercially available devices, such as wearables and smartphones, offer a variety of health features from counting steps to monitoring heart rate and from measuring oxygen levels to keeping track of night sleep quality. The list of new technologies serving medicine is ever growing and it also contains Internet of Things (IoT), Big Data science, Artificial Intelligence (AI), Robotic Surgery, Brain Sensors, and Implants among others.

Finally, in a globalized world where borders have almost been abolished, the need for a well-defined and legally binding regulatory framework for medicine and drug production is required more than ever. The first steps have been made during the last century and now more and more countries are adopting one of the international standards or vote for a national one for their own.

Therefore, the pharmaceutical industry is now regulated by the Good Practices (GMPs, GLPs, GTPs etc.), to minimize all those risks that have -or might have- a great impact on the safety of the patients/consumers. The quality of medicinal products is the base for safety and efficacy and the purpose of the regulations is to assure, that the pharmaceutical products meet the safety requirements without compromising any quality characteristics.

That is the reason why all pharmaceutical regulations are covering the whole manufacturing process, because mistakes and errors, such as “two types' mix-up” and cross-contamination, may appear in any manufacturing activities: from the used premises and starting materials to the final product and its disposal. So, multiple steps are being followed to reduce the contamination of the product and to ensure that protective measures for the external and internal conditions related to the organization are respected by everyone involved. These steps refer to raw materials, product development, technology transfer, production, storage, packaging and distribution, thus strengthening the nexus that binds the development of medicines and manufacturing activities.

GMP standards or rules are set as guidance documents from regulatory authorities or passed as laws in order to ensure that manufacturers are not driven by profit but produce medicines on the basis of human health and dignity, quality, respect and honesty.

However, both in theory and practice pharmaceutical’s benefit to society cannot be disputed. It is undeniable that the pharmaceutical industry is important to the economies of the world and for the preservation and promotion of the global health of the human society. Especially in Europe over the last century, they have contributed to a doubled life expectancy and a reduction in the mortality rate of diseases including AIDS and several cancers. Thus, whether locally or globally, the pharmaceutical industry significantly contributes to the development of the healthcare sector, technology, and the economy.

The objective of this study is to investigate the basic requirements for medical products regarding the GMP quality system and describe the complementary files of GMP guidelines that are extremely useful in the process implementation. It looks at two

major components: all different international bodies and standards that promote, support, and enforce GMP harmonization and their contribution to general guidelines and the concept of process validation.

The structure of this master thesis includes four main chapters as follows:

Chapter one is the introduction and objectives section of the dissertation. It also includes a brief historical review of medicine.

Chapter Two analyzes the pharmaceutical industry with the aim of highlighting the importance of the market and the reason for engaging with this specific subject. This will be done by using secondary data materials such as textbooks, academic journals, global and national papers and publications and unpublished materials such as dissertations and theses.

Chapter Three delves deeper in the concept of GMPs by explaining their importance, relaying the tragic events which led to the evolution of these practices, setting up some key rules and then analyzing all the different regulatory frameworks and guidelines issued by various national and international authorities and bodies.

Chapter Four lists and discusses the most important points of the guidelines -that lay on European laws and directives- for a product to enter and/or release in the European market. These general requirements are divided into four parts and nineteen annexes.

Chapter Five examines the area of validation in the pharmaceutical industry which might refer to a piece of equipment, a process, a recipe, a computer system, an analytical method etc. The study focuses on the process validation which is basically designed to be a step-by-step procedure which ensures that a manufacturing process is able to consistently produce quality products.

Section 2. Pharmaceutical Industry

2.1 Industry Overview

The term Pharmaceutical Industry refers to the group of companies which are responsible for the development, production, and marketing of both branded and generic pharmaceuticals.

It is one of the biggest industries worldwide in terms of revenue, sales, global presence, investment, and employment and is considered one of the main pillars of industrialized economies while gaining more and more significance for developing economies as well. At the same time, through innovation and by making more and more products commercially available and affordable, Pharmaceutical Industry has contributed to the improvement of the quality of living, public health, and life expectancy on average. It is characteristic that in Europe, citizens are expected to live 30 years more than they did a century ago [1]. Of course, the situation is far from ideal as the gap between developed, developing, and under-developed countries as well as between higher and lower incomes remains and inequalities in healthcare and medicinal access are present.

A well-functioning healthcare system is an irreplaceable part in every country's socioeconomic state. One of the main ingredients in that direction is the existence of an enabling environment for the Pharmaceutical Industry. Although health expenditures as a share of GDP are tending to rise in many countries, the share of those expenditures that is channeled to pharmaceutical products has remained stable and it counts for roughly 20% of total cost. Moreover, additional costs such as distribution costs, port charges, import tariffs, taxes, wholesalers, and retailers in the supply chain etc. tend to inflate the prices [2]. Especially in developing countries with a lack of solid public and private health insurance, this difference in prices comes out of customers pockets. By increasing spending in medicines and vaccines, not only access to healthcare services is being democratized but also other costs can be reduced, such as hospital costs and long care costs.

In addition, apart from helping people in terms of public health, the pharmaceutical sector is also a major employer, responsible for millions of jobs worldwide. More precisely, approximately 5.5 million people were employed inside the industry in 2017, including those working in the production of generic drugs. At the same time, indirect employment was multiple, with 45.1 million additional jobs in other sectors throughout its supply chain. If these were combined with estimated 23.7 more million jobs that are generated in other sectors like retail and childcare, a total of around 74.3 million employees were affected directly or indirectly [2].

Pharmaceutical Industry plays an important and crucial role in global economic activity. It is estimated that industry scored a total worldwide revenue of 1.24 trillion USD, while having a total value of 6.65 trillion USD (5.65 of which were generated by publicly traded companies). In order to put those numbers into perspective, if the Pharmaceutical Industry was a country, it would be the fifteenth biggest economy [5].

As shown in the table and diagram bellow, pharma sector is the third highest value sector, scoring under only Banks, Insurance and Finance and E-Commerce and Internet Services, while having tripled its value since 2003.

Rank	Sector	Public Market Value ($) Trillions
1	Banks, Insurance & Finance	18,5$
2	E-commerce & Internet Services	6,0$
3	Pharmaceuticals (public companies only)	5,65$
4	Software	4,2$
5	Integrated Oil & Gas	3,6$
6	Technology Hardware	2,9$
7	Semiconductors	2,4$
8	Electric Utilities	2,4$
9	Integrated Telecom Providers	2,2$
10	Automobile Manufacturers	2,0$

Table 1: Aggregated Market Value of all Publicly Traded Companies by S&P Market Group in the World's Top 20,000 Traded Companies by Market as of September 6, 2020 [5]

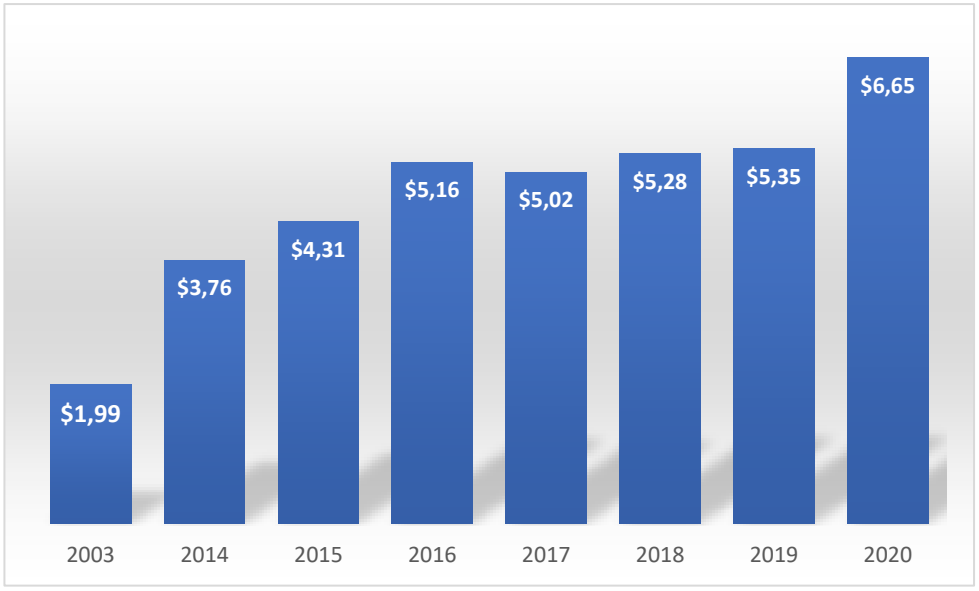

Figure 1: Aggregated Value of the Global Pharmaceutical Industry 2003 to 2020 (USD Trillions)

As expected, not all markets are the same. Sales are not equally distributed around the globe. More specifically, United States are leading world consumption with 49% of global revenue, followed by Europe with 23.9% (this amount goes up to 63.7% and 17.4% respectively when it comes to sales of new medicines) [1].

Today, the world has become multipolar, and markets and economies are changing rapidly. Emerging economies like China, India and Brazil are growing rapidly. From 2015 to 2020, these markets grew by 4.8%, 10% and 11.3% respectively when on average the top 5 European economies grew by 5% and US by 4.9% [1]. As a result,

certain aspects of economic and research activities have started to migrate from western developed countries to these new markets and this is believed that it will only get more intense in the foreseeable future.

Another interesting statistic to look upon is the one regarding the different kind of drugs being consumed per region. Some differences can be recognized, depending on cultural differences, local diet and level of access to food rich in nutrition. Although some kind of differentiation is present, certain patterns can be recognized. In OECD countries (38 member countries of the Organization for Economic Co Operation and Development which as of 2017 comprise 62.2% of global nominal GDP), between 2000 and 2017, consumption of cholesterol lowering drugs almost quadrupled, antihypertensive pharmaceutical consumption nearly doubled as well as the one of antidiabetic medicines and finally, antidepressants usage doubled as a result of depressions recognition followed by changes in guidelines and therapeutic treatments offered [3].

There seems to be a direct link between the most common causes of death worldwide and most consumed drugs. In the diagram bellow, it is evident that cardiovascular diseases are responsible for more than 30% of global annual deaths, followed by cancer and respiratory diseases. As a result, besides musculoskeletal drugs being the largest pharmaceutical market worldwide, sales for these categories were ranking at the top of the table, with cardiovascular, oncological and anti-infective drugs scoring the second, third and fourth biggest revenues [3].

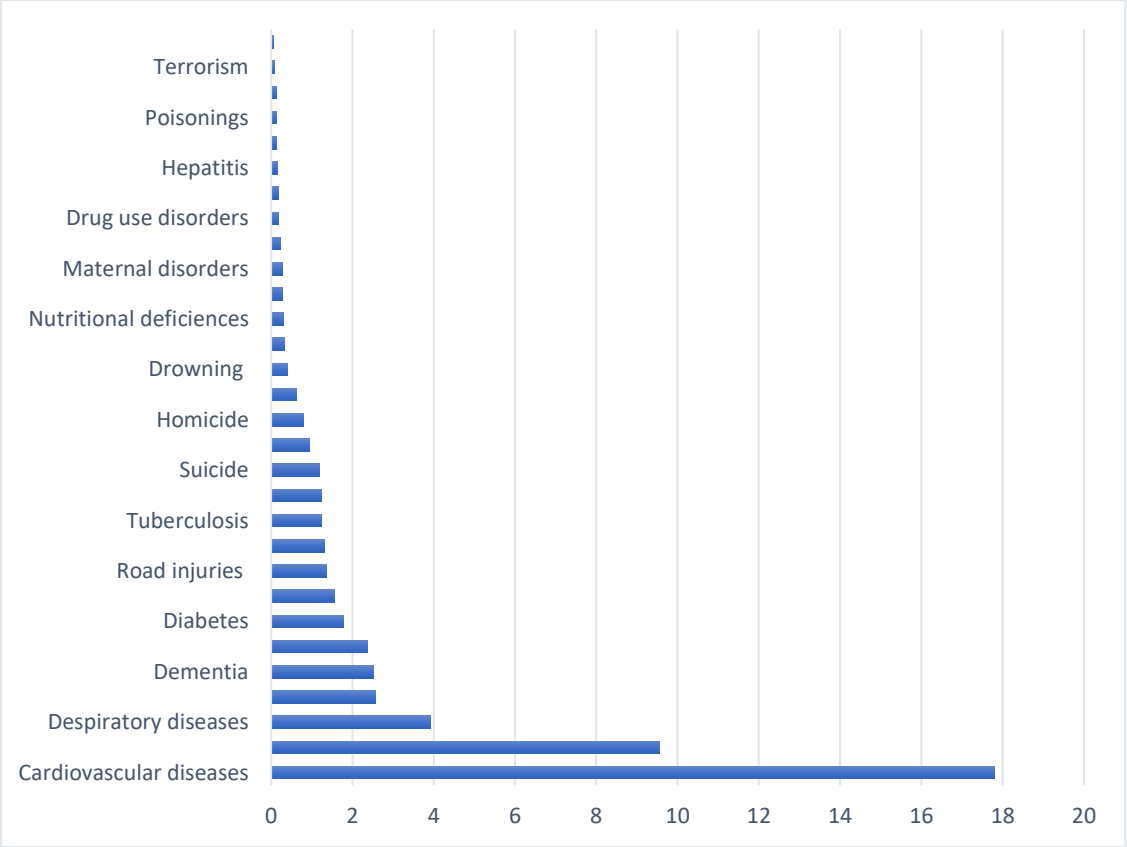

Figure 2: Breakdown of Global Deaths by cause, 2017 [3]

As mentioned above, pharmaceutical industry is highly innovative. In fact, it is the sector that invests the most in Research and Development (R&D), both in terms of total

value and percentage of net sales, even during the global economic crisis. Billions of dollars and thousands of scientists' hours are spent and as a result the limits of science are being pushed while new and more efficient products are reaching the market.

As shown in figure 3, the expenditures in most of the countries that Pharmaceutical Research activities are based, are rising throughout the years to even bigger levels. It is estimated that USD 179 billion were spent worldwide for R&D purposes in 2018 [2]. At the same time, there has been a US dominance in the field for the past decade in that particular field.

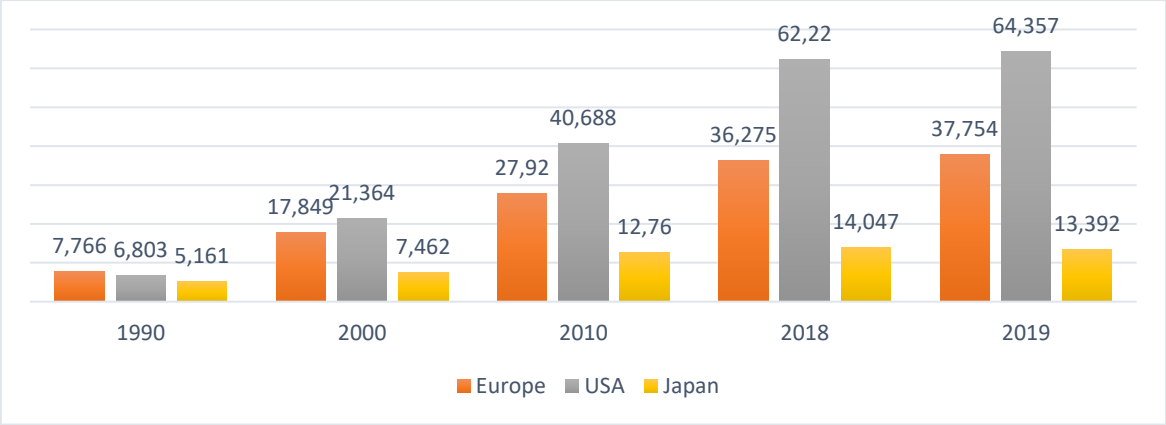

Figure 3: Pharmaceutical R&D Expenditures in Europe, USA and Japan (Millions of National Currency Units), 1990 – 2019 [1]

These high expenditures, put Pharmaceutical Industry at the top of all industrial sectors, even above the software and computer services or other research focused ones, like technology hardware or automobiles and parts, in terms of R&D as percentage of net sales for 2019.

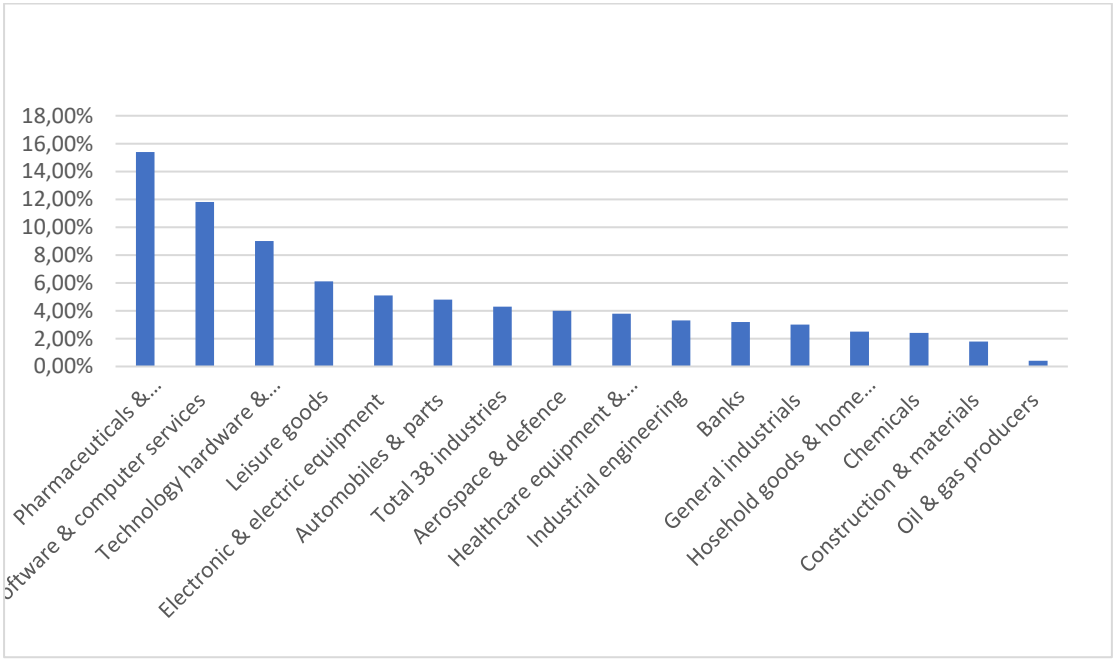

Figure 4: Ranking of Industrial Sectors by Overall Sector R&D Intensity (R&D as Percentage of Net Sales – 2019) [1]

The reasons for the need of these very elevated expenses can be found in the process followed for the discovery and marketing of a new drug. The decision on which substances will get furthered researched, based on preliminary data, contains a high risk and can easily lead to a dead end, having consumed big amount of money on the way. It is estimated that, on average, only one to two out of 10,000 substances that are synthesized in the laboratory will eventually succeed in all stages of the development process and will make it to the market.

The cycle of life for a new drug begins with the patent application, followed by the pre-clinical development, which contains assessments regarding acute toxicity, pharmacology, and chronic toxicity. If the drug is deemed safe it moves to the clinical trials. Clinical trials take place in 3 different phases with different numbers of patients taking the drug or a placebo and then monitoring the side effects that may occur. Moving forward, if the pharmaceutical product passes all 3 phases of human tests it takes marketing authorization and can then be priced and put to market. This process can take up to 13 years and bring the cost for the development of a new pharmaceutical entity to USD 2.558 million (in year 2013 dollars). Of all the different phases a new product goes through, the 3 stages of clinical trials make up to almost 50% of the total cost, compared to around 16% for preclinical stage and little more than 11% for the Pharmacovigilance phase, which is necessary after the commercial release of new products, in order to monitor potential new negatives effects that may arise after massive consumption of the drug by the general population [1].

These extensive costs and time requirements only allowed for 59 new medicines to launch in 2018 while more than 8,000 compounds are at some point of the development stage today [2].

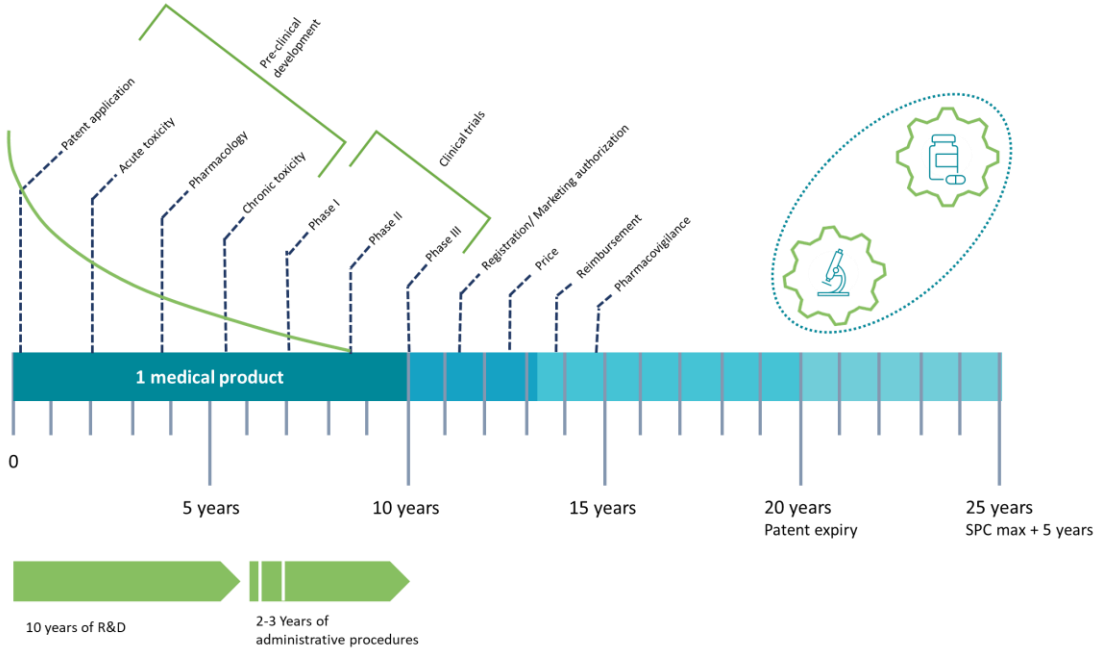

Figure 5: Phases of the Research and Development Process [1]

Even though Pharmaceutical Companies take upon them such a big risk and R&D cost, it contributes for only 2/3 of the final price with wholesalers, pharmacists and other

retailers and distributors alongside the state, make up for approximately 1/3 of the retail price.

Figure 6: Breakdown of the Retail Price of a Medicine in Europe for 2019 [1]

As it is evident, Pharmaceutical Industry is an everchanging and constantly reshaping field. New opportunities, threats and trends emerge constantly and in a global scale. Having said that, there are some main trends that can be identified for the foreseeable future.

As mentioned above, emerging economies are getting bigger by the day and thus, a shift in market focus is to be expected. Some of portion of research and production activities of Western based companies are beginning to relocate in developing countries. Moreover, a strengthening scientific knowledge, with new technologies in the service of research and development, such as smart devices, big data science etc. is contributing to the positive momentum of pharmaceutical industry. Other factors, like the growing demand for medicines and global trade liberalization, are also helping towards that direction. On the other hand, tighter regulations are getting in effect in an attempt to safeguard from errors this sensitive area of products and are making market conditions more difficult for pharmaceutical companies at the same time.

2.2 PEST Analysis

A PEST analysis is both a business analysis and a management method. The term PEST itself is an acronym for Political, Economic, Social and Technological. By analyzing these factors in a specific market, you can foresee the impact they are going to have on a business operating inside this market and act accordingly in order to achieve the goals set.

Usually, PEST is used in a well-defined and compact market (typically geographical), where the above four factors are common throughout the market. Because the Pharmaceutical market, as it has been established, is a globalized industry, with many of the big companies operating on a multinational level, it is not possible to hold a PEST analysis for the entire sector. What can be done, is to specify the elements which constitute each one of these four factors and which decision makers must look to identify in the specific external environment that their company operates.

<u>Political</u>

- State laws and ministerial decisions

- Legislation regarding monopolistic competition, protection of the environment or government contract policy
- Legal framework for the technology being used in Pharmaceutical products production
- Labor legislation
- Existence of political stability versus uncertainty
- Level of state intervention
- Taxation criteria
- Special motives offered for companies operating and investing
- Unique internal trade regulations
- Regulatory bodies

Economic

- Current state of national economy combined with future forecasts
- National Gross Domestic Product (GDP)
- Inflation rate
- Unemployment rate
- Purchasing capabilities of consumers in the market
- Government health expenditure's structure
- Taxation scheme
- Interest rate spreads
- Factors influencing offer and demand
- Native currency rate

Social

- Demographical trends, like population increase or decrease, birth versus death rates etc.
- Lifestyle trends (exercising, diet habits, healthy day to day approach etc.)
- Consumerism
- Educational level of citizens
- Social Media and Public figures influence
- Advertisement
- Role of women and minorities in society
- Level of urbanization

Technological

- Current available technology
- National expenditures for research
- Industry investments in R&D
- Patent protection legislation
- Knowledge transfer rate
- New production methods
- Production improvement through atomization

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Section 3. Good Manufacturing Practices (GMPs)

3.1 GMPs Definition

Good Manufacturing Practices (GMPs) refer to the minimum standards that a medicines manufacturer must meet in their production processes. They are regulations that describe the methods, equipment, facilities, and controls which are required for producing human and veterinary products, medical devices and processed food [7].

GMP requirements were laid out in a flexible or even abstract way in some cases, in order to allow individual manufacturers to decide which is the most suited path for each unique company to achieve the intended demands. These must have conditions, cover areas such as personnel qualification, record keeping, sanitation and cleanliness, complain handling, equipment verification and process validation.

It is important to underline that GMPs are not just a set of industry best practices. They have the force of law. A company's failure to comply with these regulations means that it's product is deemed "adulterated" and can be seized and destroyed while legal actions can be taken against the company and its management.

GMPs are built around a quality approach to manufacturing. They intend to minimize if not eliminate errors, mix – ups and contamination cases while successfully managing risk. Through the compliance with this set of practices, the produced product acquires proven strength, identity, safety, purity and quality.

Even though, as have been said, Good Manufacturing Practices only represent a minimum mandatory required standard, because of the benefits that follows the application of them, most of the big manufacturers already implement comprehensive modern quality systems and risk management approaches that exceed these minimum set of standards by far [9].

Often, GMPs are referred to also as cGMPs with "c" standing for current. This addition is supposed to emphasis the dynamic nature of these expectations. As science and technology advance, more, new and better capabilities become available and better understanding is achieved. At the same time, potential new emerged weaknesses, unveil areas needing reevaluation, improvement and / or update and serves as valuable lessons learned. Through this ever changing – ever evolving framework, it is ensured that the production of a very sensitive category of consumer good, is always taking place ruled by the latest standards.

3.2 The History of GMPs – A Series of Tragic Events

It is very common for a person to get lost in an everyday routine. It is even easier to act in a "business as usual" way or get lost in the "inertia of status quo". Reforming can be hard and sometimes only a remarkable shock is capable of setting in motion the wheels of change. That being the case for an average person, big and meaningful changes in legislation or in a regulatory body require very specific and mature conditions, just like the ones following a tragic event. Such is the story of GMPs. A series of tragic events.

As discussed in the previous chapter, history of medicine goes a long way back. But until the early 90s, pharmaceutical market remained highly unregulated. It wasn't unheard of for someone to sell homemade remedies out of the back of a wagon, made of unknown ingredients, sold in an unmarked bottle, claimed to cure everything from headache to cancer. This has, as expected, led to many devastating incidents. And with industry getting modernized and production rising, the numbers of people affected were now way bigger than before.

One of these unfortunate events took place in 1902. One diphtheria antitoxin product, made by blood harvested for a tetanus infected horse, got contaminated with live tetanus bacilli and eventually led to the death of 12 children. As a response, Congress voted the "Biologics Control Act", which required companies to perform extensive testing for purity and strength prior to drug release.

In 1905, a book by Upton Sinclair was published under the title "The Jungle". The book's main purpose was to highlight the dehumanized conditions under which laborers, mainly immigrants, worked in the Chicago meat packing industry. The book made a huge impact on USA's society and brought to light the unsanitary conditions where meat was produced before ending up to consumers table, cases of expired, rotten or diseased meat being sold and instances when remains of rats were ended up into the minced meat machine or even human remains by some unlucky worker, like a finger lost by a slicing machine. Public uprise and dissatisfaction led Congress to pass the "Pure Food and Drug Act" one year later in 1906. It was the first time that selling adulterated food became illegal. At the same time, misbranding was forbidden, and labelling had to be truthful from this point after. In order to monitor companies' compliance with the newly voted legislation, the first government regulatory agency for this purpose was founded. This agency is now known as United States Food and Drug Administration (FDA).

It was in 1933 that the, relevantly newly founded FDA, published its exhibit of dangerous food, medicines, medicinal devices and cosmetics. In what it became to be known as "The America's Chamber of Horrors" they were included, among others, lotions and creams that led to mercury poisoning, a specific eyelash that blinded women, a weight loss drug that caused death and a womb supporter that also was widely used as a contraceptive, that could puncture the uterus. This report made clearer the extent of problems caused in the general public by unregulated medicinal products.

Two years later, a sulfa drug (at the time sulfa drugs were considered "miracle drugs") that was produced with the addition of diethylene glycol (a poisonous solvent used also as anti – freezer), was accountable for the death of 107 people, many of whom were children. Once again, following another tragic event, Congress passed the "Federal Food, Drug and Cosmetic Act" in 1938. This act broadens the jurisdictions of FDA who now could implement frequent factory inspections, determine required standards, apply penalties for misconduct or even move forward with criminal prosecutions and the ability to seize and destroy any possibly dangerous product. The new act also introduced cosmetics as a category of interest that was now inspected by FDA.

Some level of requirements had been set at this point but yet another incident came to stress out the weak spots in the regulatory framework. In 1941, almost 300 people were

either killed or injured by a sulfathiazole tablet that has been tainted. FDA responded quickly by doing an in-depth revision of the manufacturing and quality control requirements. These stricter requirements were the precursor of Good Manufacturing Practices.

Moving forward, during the 60s, Thalidomide got to market. It was a sleeping pill that also treated morning sickness and was widely used. It was later found to having devastating side effects. More specifically, the drug caused deformities in developing fetuses and by the time it got out of market more than 10,000 cases have been reported. These numbers refer to Europe alone as the drug never made it to US market thanks to an inspector not giving permission. This inspector was awarded with the President's Distinguished Federal Civilian Service Award, the highest honor that a government employee can gain as a civilian, by President Kennedy, marking the importance and impact of a proper regulatory monitoring and inspection. This case galvanized public opinion and paved the way for the first Good Manufacturing Practices for finished Pharmaceutical to be made final in 1963.

More than ten years later, in 1978, GMPs were expanded again to include also medical devices for the first time and in 1979 Good Laboratory Practices (GLPs) were also made final.

Regulation was beginning to get more precise and to include more and more aspects of the production and distribution as well as more product categories. In that context, in 1980, Congress voted the "Infant Formula Act" after a number of babies got ill from a cream lacking specific nutrition. This Act gave FDA the ability to enforce standards and specify nutritional requirements for every commercial formula for infants.

In 1982, one major incident took place. It all began with the death of 7 people after having consumed Tylenol, an acetaminophen capsule. Tylenol was one of the highest selling drugs and was producing vast profits for the producing company. As a result of this tragic event, one of the biggest recalls in the history of Pharmaceuticals took place with 31 million bottles of Tylenol coming out of the market. After careful investigation cyanide was found in some capsules. Official findings talked about a criminal tamperer who was never found and prosecuted. In order to avoid similar cases in the future, FDA introduced new tamper – resistant regulations and incorporated them into existing GMPs. At the same time, Congress passed the "Federal Anti – Tampering Act" in 1983, making an official crime to tamper with any packaged consumer products.

The decade of 80s was a particularly good decade for the GMPs. During this time, FDA began publishing a series of guidance documents, clarifying different aspects of the regulations, and giving advice on how to properly implement the requested requirements. On example of such document was the one published in 1987 regarding the principles of process validation. These guidelines had a major effect and shaped the interpretation of GMPs to this day.

In 1990, a new Act was voted, in order to include also medical devices in FDAs jurisdiction. This was the "Safe Medical Devices Act", and it gave authority to FDA to dive into Research and Development (R&D) regularly and also to incorporate preproduction design standards and controls into GMPs. It was in the context of this

Act that in 1996, after having been convicted for conspiracy to defraud FDA, 3 former executives of a company that was producing balloon heart catheters were sentenced into 18 months in prison, followed by 2 years of supervised release. This company sold illegal heart catheters. After receiving a note from FDA informing them their product lacked license, the company rebranded the catheters two times and continued selling them without official approval. At the same time, reports for malfunctions, obtained even through illegal clinical trials, were concealed from authorities. These criminal actions resulted in 1 death and 20 emergency heart surgeries.

FDA in USA led the way in many cases in terms of regulatory requirements for the Pharmaceutical Companies but at the same time different countries enforced similar national standards. With the Pharmaceutical industry getting bigger and more globalized and with producing companies operating in an international level, the need for harmonization became apparent. Europe and Japan agreed upon a common ground and US, even though reluctant at first, had no choice but to join. As a result, in 2001, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) Q7A took place and introduced what is now considered the de facto manufacturing standard for Active Pharmaceutical Ingredients (APIs).

One year later, in 2002, FDA started using a new technique for routine drug manufacturing inspection. Each inspection must now focus on more than one system, with one being mandatorily the quality system and the others varying from facilities, equipment and materials to production, packaging, labeling and laboratory controls. Based on this new approach, if even one system is out of control, then the whole company is out of control and must take immediate corrective actions to become compliant with GMPs again.

Looking back, it is evident that there is a direct link between the tragic events of the past and the topics that GMPs covers. Some examples are the conditions in the Chicago meat packing industry and sanitation and cleanliness area, the Tylenol tampering case and packaging and labelling, and the list goes on, the pure management calls in the case of heart catheters and personnel qualification and the list goes on.

As we are getting closer to today, GMPs are constantly proving their value, with the biggest evidence being the absence of tragic events to the extent that has happened in the past. Pharmaceutical production is now more regulated than ever, but the very essence of Good Manufacturing Practices lies in the spirit of continuous improvement. In this spirit, it is useful to examine current and future trends.

Firstly, industry is moving away for the end point control logic of the past and towards the quality by design approach. Big companies are adopting a quality system that focus on built in quality form end to end. From R&D to production and form packaging and labeling to retail sales. Built in quality means to ensure it in every step. This can be achieved through well designed and defined processes and by promoting innovation. The idea of “better do it right in the first place” is gaining ground by the day and this is reflecting on GMPs.

At the same time, regulatory bodies must continue to keep in touch with every new information coming out of the scientific community or the production and being effective and swift into incorporating these new data inside current standards.

Finally, as mentioned above, Pharmaceutical Industry is a huge and globalized industry. Big international companies can have their R&D, clinical trials, production, and final market all in different countries. Besides all the efforts that have been made, many countries continue to have national standards for manufacturing and marketing pharmaceutical products. As a result, it is not uncommon for some companies to use this in order to bend the rules. For example, R&D may take place in a very developed country with high scientific production, clinical trials happen in a part of the world were rules for tests on animal or people are looser, production located in a region with low labor costs or less strict legislation regarding ingredients and production itself and the final product be marketed wherever the demand and the buying power is strong while taxation or import fees are low. Global efforts are in place, in order for an understanding to be reached between more countries and federations and for the harmonization of Good Manufacturing Practices to be broaden.

3.3 The Necessity of Good Manufacturing Practices

Good Manufacturing Practices, represent a complete and thorough set of rules which, if applied correctly, will lead to a well-regulated and controlled production.

The term quality, when used in the pharmaceutical industry, is referring primarily to the safety of the product and only after this is secured to its efficiency. By applying the principles and guidelines of GMPs, optimal control over production is gained and the overall risk gets minimized.

One of the biggest concerns that a company must face when thinking about applying GMPs to its operations, is the cost. Total cost of compliance can rise to 25 percent of the total budget, absorbing one fourth of the expenditures. Even though these worries are perfectly justifiable, they are a short-sighted way of doing business. An unregulated production can easily lead to tragic accidents as the ones mentioned above. Even if human lives do not get lost, the fines, sanctions, or even legal measures that authorities and regulatory bodies can impose, will eventually elevate the cost for the company to much higher levels. [20]

Until relatively recently, quality control in the pharmaceutical production, used to take place in the form of final testing of the product. This method cannot ensure quality, partially because of the small samples upon which it relies. Errors that may occurred in previous steps of the production, or even possible contaminations, can go undetected. As a result, quality must be built in every process and operation as well as the production as a whole. Good Manufacturing Practices enables the company to achieve this level of quality and minimize risk by eliminating errors and contaminations. [7]

The unparallel importance of quality in the sector, is underlined by the fact that, in the founding act of the World Health Organization (WHO), the necessity of quality was explicitly phrased and demanded inside article 2 of the constitution that lays the foundation for its operations to this day. To ensure quality and assist the way of

achieving it, developing international standards regarding Food, Pharmaceutical and Biological products, was named as one of the organization's core functions and responsibilities.

It is easily understood that pharmaceutical products are a very sensitive commodity. That is why, national, and international regulatory bodies, have set and defined very strict standards and requirements, regarding every aspect of their production. Complying with the GMPs, is the easiest way to meet these requirements. In a way. GMPs are best practices, based on prior gained knowledge, that acts as guidelines, in order to secure compliance with safety and quality standards. [20]

These days, consumers learn to require only the best in terms of quality and companies strive to find new ways to go the extra mile and add value to their customers, creating a sustainable competitive advantage. One of the many differences between pharmaceutical products and other goods, is the level of knowledge and means required in order to evaluate the commodities found in a drugstore. Consumers are not able to use their own senses to perceive if what they buy or what the doctor subscribe is in fact safe and effective. To some extent, not even medical practitioners, with the right to subscribe, can be one hundred percent sure. This is because of the information gap that exists between the industry, the medical practitioners, and the consumers. Big Pharmas, through extensive research and development programs and investments, are the main source of knowledge generation. Invoking copyrights, patents and competition, the main part of these information is getting withhold. Doctors and customers are being asked to place their faith in a product, based only on a list of ingredients. Inside this context, governments and regulatory bodies have the responsibility to bridge this gap, protecting the public health at the same time. Good Manufacturing Practices represent the way of achieving this. Through them, pharmaceutical companies, are obligated to keep information and provide them to the officials, in a way that is well documented, retrievable and / or reconstructable. [13]

It is important to highlight the importance of the bellow. Pharmaceutical products is something that is, in many cases, administered to already sick persons, with lowered metabolism who can easily regress or relapse if they consume something of doubtful origin and quality. At the same time, the very nature of these products calls for a zero deviations approach since the molecules of which they consist of are not part of a regular metabolic system. Moreover, the pharmaceutical industry is one of the most globalized and their distribution channels expands across the world. As a result, every negative impact will not be localized and can have unpredictable consequences to a number of different places and people. [14]

Another advantage of having a production that operates inside a controlled framework is the consistency of the product's quality. As a result, rejects and recalls gets reduced, bringing down all relevant costs. At the same time, the image and reputation of the company gets empowered, leading to higher levels of trust and loyalty towards the brand.

A company which has proven itself through the systematic use of GMPs, can also benefit from the competitive advantage that comes alongside. Many countries, especially in the West, impose very strict regulations to entities that manufacture or

trade sensitive products inside their jurisdiction. Also, global organizations, like WHO or UNICEF, who often buy pharmaceutical products in order to donate them through campaigns to third world countries, only buy from sources, certified for their use of GMPs. Therefore, complying with GMPs guidelines, opens up new opportunities for a company in terms of new sales and exports.

The basic requirements that need to be met in order for the GMPs to become common practice in a global scale and to be applied in an effective way, have been laid out in the joint statement issued between The International Pharmaceutical Federation (FIP) and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). In this shared document, both parties agreed upon a common goal that is to protect the well-being of the patients by producing safe and efficacy products of good quality. At the same time, the need for a regulatory framework was acknowledged, with the note that this framework should be applicable both for branded and generic products. [10]

The two Federations, recognized four basic pillars, necessary for the final success of Good Manufacturing practices:

- There must be a strong commitment to GMPs on behalf of the manufacturers
- A good regulatory framework must be designed, which will include
- Effective and comprehensive regulatory procedures
- An effectual inspection and enforcement mechanism, followed by the political will to implement it, must be in place [10]

3.4 The Ten Golden Rules of Good Manufacturing Practices

The regulatory framework of Good Manufacturing Practices can be very complicated and even overwhelming for a company that wants to comply with them. There are many different international legislations from a number of different organizations and institutions and almost every country enforces a set of rules on its own.

All these different GMPs present common elements as well as unique points. The most important of them will be analyzed in depth in the next subchapter. Here, an attempt is

being made to gather 10 “Golden Rules” that permeate all GMPs and bring together their essence and spirit.

Golden Rule #1	Get the facility design right from the start
Golden Rule #2	Validate process
Golden Rule #3	Write good procedures
Golden Rule #4	Identify who does what
Golden Rule #5	Keep good records
Golden Rule #6	Train and develop staff
Golden Rule #7	Practice good hygiene
Golden Rule #8	Maintain facilities and equipment
Golden Rule #9	Built quality into the whole product lifecycle
Golden Rule #10	Perform regular audits

Figure 7: The 10 Golden Rules of GMPs

Golden Rule #1: Get the Facility Design Right from the Start

This is the basis of any company which wants to operate in accordance with GMPs. If a production unit is being built from scratch a great attention should be given to the layout and in existing facilities it is sometimes important to take a step back and even reconsider the whole production area if needed.

In a well-functioning facility, the layout must follow the sequence of operations alongside the production line. If this is done, productivity will be enhanced through the elimination of unnecessary traffic and the possibility of errors and contaminations, due to mix ups of materials in different production stages, will be minimized.

Equipment must be selected carefully in order to be suitable for its intended use and then placed in a way that it will be easy to be cleaned, maintained and repaired if needed. In addition, instruments and machinery used for pharmaceutical productions must be non-reactive, additive, or absorptive. Appropriate calibration is also essential.

At the same time, environmental conditions should be always checked. Parameters, such as humidity, temperature, lighting, air and water quality and ventilation, must be monitored and regulated in accordance with the process standards and materials nature.

Golden Rule #2: Validate Processes

Operations can be perfectly designed, and facilities can be constructed in a state-of-the-art way. After this preliminary step though, it is important to ensure that processes and equipment are doing what they were designed to do and even more, in a consistent way.

This is called validation and it is necessary in order to control critical aspects of the operations.

Each validation activity must be well defined and planned in dedicated protocols and consistently documented. In order to maintain this "validated state", whenever a change occurs, all appropriate testing must be made anew.

There are three different types of testing used. The Installation Qualification (IQ), which is used to ensure that new equipment is installed properly, the Operational Qualification (OQ), that then tests if the equipment operates the way it should and finally the Performance Qualification (PQ) which is a proof of the product being produced consistently according to specifications.

Golden Rule #3: Write Good Procedures and Follow Them

When producing such a sensitive good as a pharmaceutical product, consistent quality must be secured. Because of that, it is important that everyone understands what is expected of him to do and the proper way to do it. Moreover, this must be done through a well-documented procedure and not by experience being passed down.

There are four different kinds of documents that are usually used in the pharmaceutical sector. The Specifications, which list the quality requirements that the final products must meet, the Operating Instructions, where certain steps for completing specific tasks are analyzed, the Operating Procedures, which gives more detailed instructions for specialized assignments and finally the Records, inside whose, a history of every batch is being kept for audit purposes.

When writing procedures, some things must be kept in mind. A good procedure should be clear, with all the necessary information given in a brief way (for example via the use of bullets, tables, diagrams etc.) and the educational level of the final reader needs to be the guide for the language used.

It is very important that all the procedures used, are being followed invariably. In many cases, a step of a procedure may seem like an unnecessary waste of time in the eyes of a machine operator. Nonetheless, proper checking should ensure the universal application of the official procedures.

Golden Rule #4: Identify Who Does What

Elaborate job descriptions should be compiled for every role, defining job tittle, job objective, specific duties and responsibilities and required skills. These jobs descriptions should be part of the organization chart of the company and be displayed to everyone through specific communication channels, for example the corporate intranet. Proactive measures must be taken in in order to avoid possible gaps or overlaps in responsibilities.

Golder Rule #5: Keep Good Records

As already mentioned, good record keeping is an essential part of Good Manufacturing Practices, that provides a detailed history of every batch and the following distribution and enables the occurrence of internal or external audits to verify that procedures are under control and followed appropriately.

Some examples of records that can be kept in a pharmaceutical company are product master records, batch or manufacturing records, material / component control records, personnel records, training records, equipment logs and cleaning logs.

At the same time, keeping good history of your production, offers another advantage, that of the traceability. If a flawed product is found before or after market release, the specific batch can be recalled instead of the whole production and the step where the error occurred can be found and fixed.

Golden Rule #6: Train and Develop Staff

People are the essence of a company. If they were to perform on a basis inspired by GMPs culture, then they should be provided with the right tools and knowledge to successfully complete their tasks.

Extensive and continuous training should be an integral part of the company's business model. Specific training for each role must be a given practice and additional training based on Good Manufacturing Practices can help raising awareness for the importance of producing the right way.

After assuring that every employee has access to sufficient training, a system of job competence monitoring should be installed. Annual performance reviews, based on key performative indicators must take place in order to periodically review the progress of the staff and identify areas of improvement. Financial or material compensation as a bonus for goals achieved can be given and work plans for future actions can be set.

Golden Rule #7: Practice Good Hygiene

When producing pharmaceutical products, avoiding possible contaminations is one of the most important quality parameters. In order to reduce the risk of contamination, a thorough sanitation plan is necessary. This plan must be always followed by everyone since the cleanliness standards can be met only with the participation of every person involved in the production process.

The measures that should be followed can be as simple as maintaining personal hygiene, avoiding coming to work when ill, removing and storing trash appropriately, not eating, drinking, or smoking inside facilities etc. All the above may seem like common sense but getting everyone to follow them in an everyday basis may prove challenging.

Golden Rule #8: Maintain Facilities and Equipment

Very often, factories producing pharmaceutical products operates on 24 hours 7 days a week schedule. This nonstop production can weary down the machines used. As a result, a solid maintenance schedule should be in place. Proper maintaining the equipment, maintain the "validated state" previously mentioned, reduces the risk of possible contamination, and prevents the breakdowns that can be costly both financially and in terms of time lost.

It is very important to keep records of every scheduled or emergency maintenance. Information such as when was the equipment last used, what for, when was last cleaned, inspected, or repaired, who maintained the equipment, how and what was used for the

task, when was the last calibration taken place etc. needs to be logged in a master record archive.

Golden Rule #9: Design Quality into the Whole Product Lifecycle

The quality control department of the pharmaceutical companies perform regular inspections. Although, these examinations take place mainly on samples of the final product which are selected based on statistical models. This procedure reduces the risk of releasing a flawed product on the market but cannot inspect each production step.

To ensure consistent quality, effective controls must be evident throughout the lifecycle of the product. The four main areas which must be constantly monitored are the specification of the components that enters production, the manufacturing process, the packaging and labelling of the final product and the storage and distribution channels.

Golden Rule #10: Perform Regular Audits

In most cases, external audits take place on a regular basis by regulatory bodies to inspect GMP compliance. In order to prepare for these outside inspections, in house audits can take place even more often as a proactive measure and corrective actions can be applied where errors are located. [15]

3.5 International Regulatory Framework Regarding Good Manufacturing Practices

The international regulatory framework regarding Good Manufacturing Practices can be very complex. There are numerous legislations and guides for their implementation and a great number of national and supernational regulatory bodies who enforce them.

A regulatory body is very similar to a professional body, except that it is not a membership organization, and its primary mission is the protection of the public. In contrast with professional bodies, a regulatory body is established on the basis of legal mandate and has executive function. It can impose requirements, restrictions, conditions, set standards regarding any activity, secure compliance or enforce. [14]

During the years passed, there have been significant attempts to unify global pharmaceutical market and to harmonize different legislation frameworks. These efforts have led to a much more compact market, but many more remains to be done.

Bellow follows an analysis of the most important and used Good Manufacturing Practices as well as of the authorities which inspect and enforce them.

3.5.1 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, or ICH for short, is a special project, conceived by the European Union in 1980s with the goal to push the industry towards a single market approach.

Preliminary discussions were held between EU, Japan, and the USA, with the latter being the most reluctant. An agreement was reached nonetheless during the WHO conference of 1989 in Paris. Based on this agreement, ICH was finally born next year, in Brussels. [14]

Six different entities were originally involved in the founding of ICH and are listed below:

- The European Commission
- The European Federation of Pharmaceutical Industry Association
- The Japanese Ministry of Health and Welfare
- The Japanese Pharmaceutical Manufacturers Association
- The United States FDA
- The United States Pharmaceutical Manufacturers Association

Moreover, 3 observers were listed, representing the non-ICH countries, WHO, European Free Trade Association and Health Canada. Finally, the International Federation of Pharmaceutical Manufacturers Association provides a secretariat for the ICH. [13]

As of October 23rd 2015, ICH is filed as an international non-profit Association under Swiss Law. In addition, the Association has expanded to include two more Standing Regulatory Members. Health Canada (Canada) and Swissmedic (Switzerland). Also, ICH regulatory members list, now consists of an additional eight bodies relayed here:

- ANVISA (Brazil)
- COFEPRIS (Mexico)
- HAS (Singapore)
- MFDS (Republic of Korea)
- NMPA (China)
- SFDA (Saudi Arabia)
- TFDA (Chinese Taipei)
- TITCK (Turkey) [29]

During its early years, ICH promoted the communication and knowledge exchange between the regulatory authorities of the three founding parties, together with experts coming from the pharmaceutical sector in those regions. Scientific and technical aspects of product registration were discussed as well as issues regarding the approval and marketing authorization of new medical products. [13]

The mission of ICH is to assist in the development of a pharmaceutical quality system, which can be applied throughout the product's life cycle and will emphasize an integrated approach regarding quality risk management and science. [14]

At the first ICH Steering Committee meeting, together with the Terms of Reference, the topics for harmonization were agreed. The work and actions of the ICH would focus on Safety, Quality and Efficacy. Those three pillars, represent the three respectively basic requirements which must be met for approving and authorizing new medical products. [29]

Through this harmonization, ICH is aiming to achieve a more efficient use of resources, either human, animal, or material, and to eliminate any unessential delays that takes place during the global development and distribution of new pharmaceutical products, while safeguarding quality, safety, efficacy and regulatory compliance to protect public health at the same time. [16]

This harmonization is being achieved through mutual recognition between participating regulatory authorities, based on the exchange of data and assessment reports. As a result, duplicate testing and inspection procedures are getting eliminated, the costs are decreasing and the introduction of new pharmaceutical products to the market speeds up. [13]

Throughout the years, ICH has produced several work products which cover medicinal products from end to end and incorporated them in some Quality Guidelines. More specifically:

- Stability (Q1A – Q1F)
- Analytical Validation (Q2)
- Impurities (Q3A-Q3E)
- Pharmacopoeias (Q4A-Q4B)
- Quality of Biotechnological Products (Q5A-Q5E)
- Specifications (Q6A-Q6B)
- Good Manufacturing Practice (Q7)
- Pharmaceutical Development (Q8)
- Quality Risk Management (Q9)
- Pharmaceutical Quality Systems (Q10)
- Development and Manufacturing of Drug Substances (Q11)
- Lifecycle Management (Q12)
- Continuous Manufacturing of Drug Substances and Drug Products (Q13)
- Analytical Procedure Development (Q14) [29]

Good Manufacturing Practices are being covered in Quality Guideline Q7. Quality Guideline Q10 is of specific value. It is broader than the mere concept of GMP and it includes the essence of Q7, Q8 and Q9 as well as the ISO series. This guideline provides a life cycle approach focused on three objectives. To achieve product realization, to establish and maintain a state of control and to facilitate continual improvement. [14]

Besides the above-mentioned Quality Guidelines which relate closely to GMPs, ICH also issues Safety Guidelines, Efficacy Guidelines and Multidisciplinary Guidelines.

3.5.2 European Framework

In the European Union, national authorities together with the European commission and European Medicines Agency (EMA), negotiate and formulate a legislative framework on a central level which is then in turn integrated into national law.

EMA was established by directive EC 2309/93, and it operates since 1995. Its purpose is to scientifically evaluate applications for marketing authorization and monitor the

overall medicine safety in the European Union. It is primarily a scientific body and therefore it holds no executive power. EMA serves as an umbrella organization for all individual national regulation bodies and provides evaluations which are submitted to the European Commission for approval or withdrawal. The European Commission has a dedicated committee for this purpose called Committee for Medical Products for Human Use (CHMP). [5]

At the same time, the commission serves as an intermediate between the EU and third parties, negotiating Mutual Recognition Arrangements (MRAs). MRAs is a joint acceptance of standards of GMPs and a commitment to take actions to ensure compliance. Under MRAs, the regulatory authorities of each party, accept each other's inspection reports and pretesting of imported products is not normally required.

The EU legislation is written in an abstract way, laying down the basic principles and requirements and then detailed guidance is provided through guidelines that interpret and expand the principles and essence of regulations. [8] Guidelines are then used by national regulatory authorities as a basis for inspection or when assessing applications filed by pharmaceutical companies. Alternate methods, differentiated from guidelines, can be used if equivalent assurance is provided, although this is usually avoided because of the elevated risk it contains as a practice. [5]

Each time a new pharmaceutical product needs to be registered in the European market, there are three different legal frameworks that can be applied, as established by the EU.

Centralized Procedure: This path is mandatory for the approval of biotechnology and high technology products, orphan drugs, new active substances that were not previously authorized in the EU and are meant for the treatment of HIV/AIDS, cancer, diabetes, or neurodegenerative disorders.

Decentralized Procedure: In this case the authorization is being carried out by the national agency of each member state in which the pharmaceutical distributor is seeking marketing authorization.

Mutual Recognition Procedure: If a product has already gained approval through the decentralized procedure, the company can then apply for marketing authorization accordingly in every other EU member. The country originally authorizing the drug must provide a detailed assessment report to every interested party. [13]

The legal framework that governs the pharmaceutical products disposal in the unified market is defined by the below documents.

- Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [36]
- Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use [37]
- Directive 2001/82/EC relating to veterinary medicinal products [38]
- EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use [39]
- European Pharmacopoeia [35]

Greece, as a member state of the European Union, has integrated community directives into national law. The adaptation took place with the vote of the Official Government Gazette of the Hellenic Republic Y6/75691/2004 amending O.G.G. Y6/11228/92 for harmonization with EU Directive 2003/94/EC regarding Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.

3.5.3 European Pharmacopeia

The term Pharmacopeia is referring to a book of recipes used to produce pharmaceutical products, together with instructions and requirements. Their origin can be located back to ancient times in a more primitive version. Modern Pharmacopeias on the other hand, include detailed quality prerequisites for the active substances, general requirements for the analysis and production of pharmaceutical products, monographs for certain marketed drugs and classification of products and substances to unique categories based on different forms and properties. The term monograph refers to certain articles inside Pharmacopeias which corresponds to a certain active ingredient and describe standards, preconditions and methods of quality control and assurance for it.

In each Pharmacopeia a very strict and universal terminology is being used. Historically, each country, used to develop its own Pharmacopeia with different levels of success. After World War 2, a movement for harmonization has emerged in this field also and supernational handbooks were created. The most well – known examples being the European Pharmacopeia, the United States Pharmacopeia and the Pharmacopeia issued by the World Health Organization.

The United States Pharmacopeia (USP) and WHO Pharmacopeia, contain certain tests and procedures but hold no mandatory requirements. They are a more informal and consulting document in their nature. [14]

Contrariwise, the European Pharmacopeia (EP) is a legally binding handbook that controls the quality of pharmaceutical products. It was first introduced with the first edition in 1969 and the most recent in the tenth edition of 2019. It is currently used in more than one hundred and twenty countries and contains 2462 monographs, 283 general texts and 2850 descriptions of reagents. It is applied to products designated for both human and veterinary use. The quality standards which are described are implemented throughout the whole life cycle of the drug and therefore a build in approach is used. Its legal status was established by two different EU directives, the 2001/82/EC and 200/83/EC correspondingly. [21]

As already mentioned, EP is a detailed collection of standardized specifications on the quality of pharmaceutical preparations, their constituents, and their containers. Some of these requirements may apply to more than one classes of substances and preparations simultaneously and as a result they are covered by general monographs. If the requirements need to be strict and specific, dedicated monographs are used for the particular substance or preparation in question.

Those monographs are legally binding in general but can be just informative if it is clearly stated that the text is non mandatory. Generally, the need for compliance is

deriving from the fact that a new product needs to be produced in accordance with the EP in order to obtain marketing authorization. [5]

The European Pharmacopeia is updated constantly by the European Pharmacopeia Committee which adjourn 3 times a year to review and adopt chapters proposed by experts and to decide and schedule future actions and research, based on current scientific data. The EP committee consists of a president and vice president, the members of the committee, two or three from each country and thirty nine in total, thirty observers (European Commission, WHO and non – member countries), a technical secretariat and expert committees having consulting role.

There is one main restriction in EP. It contains only a few individual final forms of dosages.

3.5.4 United Kingdom Framework

In the United Kingdom the supervisory role of the pharmaceutical market lies upon the executive body of the Ministry of Health called Medicines and Healthcare Products Regulatory Agency (MHRA). The purpose of the agency is to assess the quality, safety, and efficacy of medicines (new and existing) and grand authorization for marketing across the UK. At the same time, it conducts post marketing surveillance and oversees clinical trials for both medicines and medical devices.

MHRA consists of five separate inspectorates, tasked with monitoring the compliance of Good Clinical Practices, Good Distribution Practices, Good Laboratory Practices, Good Manufacturing Practices and Good Pharmacovigilance Practices respectively. The agency does not have the authority to provide overseas manufacturers sites with licenses but performs pre-arranged and unannounced inspections instead and focuses on products meant to be imported in the UK market. Currently, MHRA, inspect producers and distributors in countries including USA, India, China, and Japan. [13]

As expected, Brexit had a big impact on the legal framework governing the pharmaceutical market in the UK. As of January 1st 2021, EU pharmaceutical law is no longer in effect in the United Kingdom with the exception of Northern Ireland which will exit EMA on a later date.

United Kingdom Ministry of Health has designed a thorough scheme for the after Brexit handling of all legal aspects that will arise in relation to pharmaceutical market. To begin with, MHRA will become a standalone agency. All previously centrally authorized products by the European Union will convert automatically into Great Britain's catalogue of approved substances unless the producing company decides to opt out. Then, manufactures must provide baseline product data within one year. For drugs that have already been certified through the EU centralized, decentralized or mutual recognition procedures, abbreviated assessment procedures were established with a deadline of sixty-seven days for each product. Finally, in regard to pending applications on January 1st, 2021, these requests must be submitted anew to the MHRA as has been submitted to EMA. Any evaluation that has already been conducted by the EMA to this point will be considered by MHRA which will the complete its own assessment. This process has taken the name "in – flight assessment" and must be

completed in each case no later than the issue of the corresponding European Commission decision. [30]

3.5.5 International Organization for Standardization (ISO)

International Organization for Standardization (ISO) is an international standard development Organization. It is composed of representatives from the national standards authorities of each country member. All the international standards elaborated by the organization are prepared by allocated technical committees, in which every national standards body has the right to participate.

As already mentioned, the pharmaceutical manufacturing industry, is highly concerned and focused on quality and good practices. Therefore, some ISO standards are applied, together with the GMPs on different stages of the products life cycle. More specifically, there are three main standards that are mostly used in this particular sector.

ISO 17025-2017: This standard refers to good operation of a pharmaceutical laboratory. It contains requirements for capabilities, impartiality, and consistency. In order to achieve the above, a mechanism to identify and eliminate threats while making good use of existing opportunities, is called for. By following the instructions of ISO 17025-2017, effectiveness elevates, and better results are yield, cooperation and exchange of information and know how between laboratories and different agencies are facilitated and the harmonization of standards and procedures is accommodated.

Good Laboratory Practices (GLPs), as laid out in this standard or as derived from benchmarking with current best practices, are essential, and one of the main reasons is that the laboratory is part of the formulation, inspection, and certification process of the product. By applying the guidelines of the standard, the company can clarify and delimit responsibilities, establish operational rules (this, among others, can assist on an easier onboarding of new employees), improve overall quality (through Key Point Indicators, process improvement and uncertainty measurement) and boost the brand in terms of prestige and credibility.

Many of the areas covered inside ISO 17025-2017 are also examined in pharmacopeia. Some examples are issues regarding equipment, process validation and sampling. At the same time, the standard addresses a number of subjects, not present in pharmacopeia, such as impartiality, confidentiality and organizational structure, staff, resources sufficiency and facilities. It can be said that pharmacopeia focuses only on analysis and tests while ISO sets an overall framework for managing every activity of the laboratory. [21]

ISO 9001-2015: This standard is probably the most known one and it deals with quality management in general for businesses working in every sector. The basis for this management model is the Plan – Do – Check – Act approach. It is characteristic that TUV NORD has issued more than 1.1 million certificates for this standard worldwide.

Pharmaceutical companies, can use ISO 9001-2015 to reduce production and operational costs by making better use of their resources, implement continuous

improvement, enhance their reputation and credibility, and infiltrate new and untapped markets.

There is a verry limited correlation between GMPs (which are referring to controlled procedures) and ISO 9001-2015 (a general management system). In short, ISO states what needs to be done while GMPs specify how it will be done. Having said that, there are a few areas covered by the standard that are not mentioned in Good Manufacturing practices and these are the need to control procedures through a dedicated quality manual, the commitment made by the top management towards both internal and external clients and the creation and periodical update of a business plan for continuous improvement. [21]

ISO 14000: It is an environmental management system. Its aim is to minimize the harmful effects that can be caused on the environment by the company's activities. Because of the sensitive nature of the products, biproducts and wastes of the pharmaceutical industry, this standard is of great significance. If implemented correctly, can magnify continuous improvement of the company's environmental performances. [16]

3.5.6 World Health Organization (WHO)

World Health Organization (WHO) is promoting global well-being and healthy life by leading global efforts guided by science. A strong weapon in this direction is the Technical Reports Series (TRS), through which the WHO makes available the findings of different international scientific groups or experts on a vast range of medical and public health issues.

Pharmaceutical Production is covered in two different TRS. Firstly, the Annex 2 of TRS 986, lays out the main principles of WHO Good Manufacturing Practices for Pharmaceutical Products and the Annex 4 of the same TRS provides guidance on these Good Manufacturing Practices through an inspection report. The WHO framework on the subject is completed by the report issued by the WHO Expert Committee on Specification for Pharmaceutical Preparations (Currently TRS 1033). [14]

WHO GMPs and Guidelines, recommends several different types of inspections and suggest specific regulatory actions in cases of non – compliance. Having said that, the implementation of them lies with the national regulatory bodies of each individual state because they have no legal mandate on their own.

The global pharmaceutical market and production can be very complicated and demanding. In its effort to ensure a bare minimum for public health in each country and for everyone, the World Health Organization compiled its Good Manufacturing Practices in the direction of setting the most basic requirements. Hence, the result is in many cases abstract and in developed countries, consists only a subset of more detailed assurance systems. For that reason, WHO GMPs are used primarily in developing countries and this can have two different effects. Businesses which are big enough and have substantial capital reserves, invest in making their production GMP compatible and by making so they improve their operation, become more competitive and open to new markets. On the other hand, this can lead to the creation of barriers to entry and /

or to growth of smaller domestic pharmaceutical companies which do not have the same capabilities. Local based producers may be pushed out of the market or forced to attempt to acquire GMP certificates on the black markets in order to keep their operation running. [13]

3.5.7 Food and Drug Administration (FDA)

In the United States of America, the oversee and control of the pharmaceutical market, lies within the jurisdiction of the Food and Drug Administration (FDA), an agency of the U.S. department of Healthcare and Human Services. FDA, besides food and pharmaceutical products also regulate the tobacco industry. [9]

The activities of this organization are far broader than the ones of EMA. Its role and goal are to protect the general public health. More specifically, food, drugs, medical devices, biologics, animal feed and drugs, cosmetics, radiation emitting products and tobacco commodities, all fall under the FDAs umbrella. Like the European agency, FDA assesses new products on a scientific and quality base, grands marketing approval and operates post marketing surveillance. The difference is that the latter holds executive power and can impose sanctions directly in cases of non – compliance. [13]

The bureau maintains offices in strategic locations all around the world, including but not limited to China, Europe, India and Latin America and it works closely with foreign governments, industry representatives and all the strategic stakeholders. [14] Although, regarding foreign manufacturers, the inspections are focused solely on Active Pharmaceutical Ingredients that are intended for market release or are already marketed in the U.S.

FDA uses the SISPQ (Strength, Identity, Safety, Purity, and Quality) criteria as the core of its operations. Through this set of criteria, it builds systems aimed to assure proper design, monitoring and control of pharmaceutical manufacturing processes and facilities. As a result, all five standards are met, strong quality management systems are established, appropriate and safe raw materials are constantly selected, robust operating procedures are being established, product quality deviations are getting detected and properly investigated and reliable testing laboratories are being maintained. [9]

As already mentioned, FDA holds executive power and this is derived from the Code of Federal Regulations (CFR), which is a collection of final regulations published in the federal register (50 titles in total) and is a federal law. The title 21 that governs food and drugs within the United States is updated annually and then put on public review and comments for a 30-day period before becoming final. In general, EU and US regulations are relatively similar but the US one is lengthier and more prescriptive by incorporating details which in the EU scheme is included in the guidelines instead.

The US cGMPs are incorporated in four different parts of CFR title 21. The letter “c” in cGMPs, meaning “Current” is used to emphasize that pharmaceutical producers need to constantly employ up to date technologies, scientific data and systems, in order to comply with the regulations. ICH Q7 and Q8 guidance are included inside those parts.

Part 210: Includes the Current Good Manufacturing Practices in manufacturing processing, packing, or holding of drugs. It is a framework for the regulation along with some definitions. [8] It contains the minimum methods to be used, and the facilities or controls that will assure that the drug produced complies with the requirements imposed by regulation, regarding safety and that has the necessary identity and strength to meet the quality and purity characteristics that claims to possess. [16]

Part 211: Lays out the Current Good Manufacturing Practices for Finished Pharmaceuticals

Part 225: Describes the Current Good Manufacturing Practices for Medicated Feeds

Part 226: Complies the Current Good Manufacturing Practices for type A medicated articles

The above four parts are accompanied by the corresponding guidelines which aim to assist the implementation of modern quality systems and risk management approaches in order to meet the requirements of the FDAs cGMP regulations. They consist of six major sections. Management, Responsibilities, Resources, Operation Management and Evaluation Activities. At the same time, clarifications are offered, and minimum requirements are portrayed for the preparation of pharmaceutical products for human or animal use. [16]

The agency performs scheduled and unexpected audits or investigate certain leads resulting from the pharmacovigilance process. After an audit takes place, the form FDA 483 is issued. That is the "Notice of Inspection observation" sheet, which is used by an investigator following the inspection of a certain plant. It is a record of irregularities noted and possible deficiencies in the quality system while predicting new compliance issues that may occur. The pharmaceutical companies then must proceed with corrective actions.

If a company fails to comply with the cGMPs, the drug it produces is considered adulterated under the law from this point onwards. The FDA does not hold the authority to force a company to recall single batches or even the whole production of an adulterated drug but can seize and destroy it.

3.5.8 Pharmaceutical Inspection Co-Operation Scheme (PIC/S)

The Pharmaceutical inspection Co-Operation Scheme (PIC/S) was established in 1995 as an extension to the Pharmaceutical Inspection Convention (PIC) of 1970. It is a non – binding co – operative agreement between participating regulatory authorities in the area of Good Manufacturing Practices of medicinal products for human or veterinary use. There are currently fifty-four participating authorities over the world. Its primary reason is to lead the international development, implementation, and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of pharmaceutical products. [34]

PIC/S has been active in the development and promotion of GMP standards and guidance documents since its creation and issue or amend existing GMP guidance documents on a yearly basis. The main instrument of the Scheme is the PIC.S GMP

Guide which derives from the WHO GMPs and was then further developed. It is considered a pioneer in developing such documents with some examples being the Site Master File, the Recommendation on Quality System Requirements for Pharmaceutical Inspectorates and the first ever issued guideline for the Manufacturing of Active Pharmaceutical Ingredients. Moreover, it's role in elaborating a first draft of the ICH Q7A Guide on APIs which was later finalized by ICH in2000 and adopted anew by PIC/S, was pivotal. In addition, EU, which was using PIC/S guide, adopted its own after 1989 that is equivalent to the one of PIC/S and the two guides have been developed in parallel ever since (they are practically identical).

On top of the already mentioned functions of the scheme, offering training services to GMP inspectors, has been one of the core activities of PIC/S since it was initially established. This is achieved through offered seminars, a joint visits program between experienced and new inspectors, coached inspections and expert circles where experience and know how is transferred)

3.5.9 China

In a world changing ever so rapidly and a pharmaceutical market that is more interconnected than ever, GMPs are gaining an even more crucial role. West has dominated this industry in the past but emerging economies are constantly growing, closing the gap between them and the already established leaders of the sector. Pharmaceutical manufacturers coming from these countries, may use international GMPs as a benchmarking standard but are officially regulated by the national legislation. In this context, it is worth examining one of the most representative cases, the one of China.

Chinas first GMP version was issued in 1998 by the Ministry of Health. Later, in 2010, the fourth and most recent set of the Good Manufacturing Practices rules was edited, and it raised the standards while pushing the country to make rapid progress in its overall pharmaceutical manufacturing level. [31] The quality by design approach was introduced for the first time, meaning a quality control system which covers the entire process of drug design, R&D, production, testing, storage, shipment, and use. A quality risk management viewpoint throughout the products lifecycle was made possible by incorporating ICH Q9 and Q10 guidelines inside the core of 2010 Chinas GMP.

The similarities between the 2010s GMP version and the EUs one are numerous but some gaps remain, regarding the role of qualified persons, the practice of continuous monitoring, the enforcement of laboratory investigations of any abnormal test results, the existence of requirements for isolating different product lines, etc. [31]

China's will to embody best practices became apparent when it became a formal member of ICH in 2017. The most recent and drastic shift in perspective on the subject was noted in 25/09/2022. On this date, the State Food and Drug Administration issued the Notice on Learning and Propagating the Drug Administration Law of the People's Republic of China, officially announcing the cancellation of GMP and GSP certification and change the APIs and excipients to be approved together with pharmaceutical products. [32]

This may seem like a regression at first. The case is that GMP certification was thought to approve the operation up to this point. In many cases, pharmaceutical manufacturers, began to relax after obtaining the certification and the regulatory authorities had to use great efforts and resources every year in order to investigate and revoke GMP certificates of enterprises breaking the law. Now, the state's mentality is steadily transforming from stressing threshold to stressing supervision, meaning that the frequency of supervisions will increase, and unannounced inspections will take place in the daily production. [32]

Having said that, it is still hard for China to compete with well-established companies of the West unless significant improvements are made in areas such as software usage, human resources and adopting sufficient quality management systems.

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Section 4. Good Manufacturing Practices Guidelines

As already mentioned in the previous sections, pharmaceutical products that are being manufactured or marketed in the European market are regulated through a set of laws and directives. On the other hand, legislation only lays out the operational framework and portrays general requirements and quality standards. As a result, a plethora of guidelines were created, further elaborating the essence of the legal framework. More specifically, European guidelines are divided into four parts and nineteen annexes. Below, the most important points of the guidelines are relayed.

4.1 Part I: Basic Requirements for Medicinal Products

4.1.1 Chapter 1: Pharmaceutical Quality System

The core principle of this chapter is to make sure that all holders of manufacturing authorization are taking all proper measures to ensure that the medicinal products that are being manufactured are meeting the necessities for their intended use, comply with all corresponding requirements and pose no risk for the patients because of insufficient safety, quality or efficacy. In order to achieve this, employees of all departments and different levels as well as company's suppliers and distributors need to commit and participate in the process.

Firstly, the pharmaceutical quality management is being addressed. The quality management system is a very broad topic which incorporates the GMPs and covers all matters which have an impact on the final quality of the product. When creating, revising, or operating a quality management system, the size of the company as well as its activities should be considered. [1]

A well-designed pharmaceutical quality management system must make sure that constant quality of the medicinal product is ensured throughout its lifecycle by taking GMP's requirements into consideration. In order to achieve this, every production or control operation and the corresponding managerial responsibilities need to be clearly defined. Specific procedures must be established to control both supply chain and outsourced activities. At the same time, potential deviations from the defined standards should be investigated through root cause analysis and properly addressed via corrective and / or preventative actions (CAPAs). If these CAPAs are designed carefully and periodically be assessed and improved, will eventually lead to continuous improvement. The quality system is documented in a Quality Manual and calls for self-inspections or external quality audits. The ultimate responsibility for an effective quality management system lies with the senior management who must make sure that every necessary resource is being provided.

Moving forward, the quality control aspect is examined. This area is responsible for sampling, testing, organizing, documenting, and setting necessary specifications. [1] For the above to be properly executed, adequate facilities must be provided, trained personnel should be available and well-defined procedures for sampling and testing have to be in place. It is crucial that records are always maintained and checked against specification by a qualified person and no batch of final product should be released

prior to proper approval by him. Finally, during the above-mentioned process, reference samples must be kept for potential future examination.

Concerning the evaluation of the already mentioned procedures, a periodic and systematic quality review of all licensed medicinal products must be overseed with the goal of confirming the constancy of existing processes, validating the suitability of present specification, highlighting potential trends, and identifying possible improvements. [1] Indicative examples of such quality reviews are the review of starting materials, review of critical in process controls and finished products, review of every product batch that failed to meet specification and their corresponding investigation, as well as review of potential deviations and non-conformances, potential changes to processes and quality related complaints, returns and recalls. [1] Following the issuance of the above-mentioned reviews, an evaluation of the produced results must follow with the aim of identifying possible preventive and / or corrective actions.

An integrated quality management system is not sound if it does not include a quality risk management system which is a systematic process for assessing, controlling, communicating, and reviewing the quality related risks of the medicinal products. [1] It must be highlighted that quality risk management can be applied both proactively and retrospectively and must be built on scientific knowledge and experience of the processes.

4.1.2 Chapter 2: Personnel

The second chapter of the EU guidelines tackles the very important subject of personnel in the pharmaceutical industry. It is people who after all are responsible for a proper manufacturing process. Hence, there must be a sufficient and qualified number of employees to perform all the necessary tasks within the responsibility of the manufacturer.

An organizational chart must be in place, which clearly specifies the managerial hierarchy and the relationship between each role. In addition, the specific duties of each position should be properly described in written job descriptions and special attention should be given to avoid possible gaps and overlaps of responsibilities.

The senior management oversees and must appoint key management personnel, such as the head of production, the head of quality assurance and at least one qualified person and specify their unique or shared responsibilities. [2] The qualified person plays a crucial role in the production of pharmaceutical products. If a batch is not cross checked against legal regulations and the requirements of the marketing authorization for the EU states and get approval of the qualified person, it cannot be released. In addition, if the product is imported from third countries, all the necessary tests, including a full qualitative and quantitative analysis must be performed in order to make sure that the quality is in accordance with marketing authorization requirements. [2]

All personnel who are involved in the production or storing operations, who works into control laboratories or whose job may affect the final quality of the product, must undergo continuous training, the results of which, should be documented and periodically assessed.

Another very important aspect of ensuring product's quality, is the establishment of proper hygiene. To make this possible, thorough hygiene trainings should be designed to cover different needs across the company. Some examples may include but not limited to health-related procedures, hygiene practices and clothing of personnel. It is also essential for every new employee who is recruited must undergo a full medical examination. Moreover, to secure production's cleanness, every person who is about to enter manufacturing areas, must wear all required protective clothing and every practice which potentially might undermine product quality should be strictly forbidden. [2]

Finally, if the company is collaborating with external or in house consultants, they must be of sufficient experience, training, and education to offer reliable advice. Elaborate records, containing the name, address, qualifications, and the type of services provided, must be maintained. [2]

4.1.3 Chapter 3: Premises and Equipment

Chapter 3 focuses on the topic of premises and equipment. More specifically, the need for the premises and equipment to be in proper location, designed and constructed, adapted when required and maintained accordingly to serve the operations, is highlighted. [3] Their arrangement should be such as to help minimizing the risk of errors and contamination that can have a negative impact on the final quality and to assist effective cleaning and maintenance. This section is focused on five categories which are presented below.

Firstly, regarding the production area, the need for implementation of the quality risk management principles is underlined in order to avoid cross contamination. In detail, if a medicinal product presents a high-risk potential, designated facilities must be allocated for its production and packaging with entry restrictions for unauthorized people. In order to improve efficiency, the sequence of the operations must be the guide for designing production areas in a way that follows the corresponding logical order.

Storage area is the second topic that is discussed, and the focus is aimed at the need for sufficient capacity to permit a well ordered and untainted storage of the various categories of materials and finished products. Also, proper design must guarantee that receiving and dispatching bays are adequately protecting the materials from weather conditions while allowing for preliminary cleaning of the containers before use. Moreover, clearly marked quarantine areas should be in place together with separate sampling areas for the starting materials. Finally, a designated space must be created for the storage of rejected, recalled, or returned materials and products as well as highly active ones. [3]

Moving forward, reference is made to quality control areas with distinguished quality control laboratories facilities, separated from production rooms and independent areas for the protection of sensitive instruments from vibration, electrical interference, humidity etc. Also, special requirements are relayed for the operating with particular substances. [3]

Regarding the ancillary areas, there should be easily accessible and appropriate for the number of employees rest and refreshment areas as well as special rooms for clothes changing, washing and toilet usage.

Closing this chapter, the installment of the equipment is addressed. All machinery and instruments must be properly designed, placed, and maintained in a way that serves its purpose, helps to avoid cross contamination and hazard for the employees, can be comfortably cleaned by following detailed and written procedures. It is also very essential that every part of equipment which come into direct contact with the product, must not be reactive, additive, or absorptive and every instrument used for measuring, weighing, and recording should be calibrated using preset standards. [3]

4.1.4 Chapter 4: Documentation

As it has been evident up to this point, having a proper documentation process is a very crucial part of every quality assurance system and is responsible for establishing, controlling, monitoring and recording all activities which may affect the overall quality of the medicinal product in any way. [4]

Below, follows a list of the required documentation for GMP compliance.

- Site Master File: An extensive file that includes and analysis all GMP related activities [4]
- Instructions: Are divided in two types, directions, and requirements
  - Specifications: Documents which relay the full requirements necessary for the product or material to meet in order to achieve compliance. Some examples may be specifications for starting and packaging materials, specifications for intermediate and bulk products and specifications for finished products
  - Manufacturing Formulae, Processing, Packaging and Testing Instructions: Here every starting material, equipment and computerized systems are described in detail and all mentioned instructions are specified. It is important to note that these instructions must be present for every product and batch size manufactured
  - (Standard Operating) Procedures: More thorough directions for the performance of specific operations, such as receipt, sampling, testing etc.
  - Protocols: Are used to provide further instruction on performing and recording cautious procedures
  - Technical Agreements: Must be in place between contract givers and acceptors when an activity is being outsourced. [4]
- Records and Reports
  - Records: Every action taken in order to achieve compliance with GMPs is demonstrated here
  - Certificates of Analysis: A synopsis of testing results
  - Reports: Is where the conduction of certain exercises, projects or investigations alongside their results, conclusions and recommendation are documented [4]

All the above-mentioned documentation types must be well defined and assigned to a designated person or group of people as well as clearly state its location and the length

of its corresponding retention period (depending on the nature of the document). There is no mandatory form in which documents should exist and as a result they can be digital, analog or in hybrid forms. The authorized person is responsible for signing and approving documents that include instructions. In addition, all documents must be periodically reviewed and updated if necessary, making sure that the style and language used fit their intended use and concerned parties.

4.1.5 Chapter 5: Production

The core principle of a GMP regulated production is that every process should be conducted according to clearly described procedures, instructions and if required records. All incoming materials and produced yields must be checked and inventory must be reconciliated to make sure that any discrepancies outside acceptable limits won't occur.

At the same time, all mix ups and cross contamination must be avoided. In order to achieve that, all items must be accurately labeled, access to production areas should be restricted to non-authorized personnel and a zero deviation from specification policy should be applied unless specifically approved otherwise by the quality department. As expected, medicinal and non – medicinal products ought to be produced in separated areas. The potential risks of cross – contamination must be evaluated based on hard evidence such as potency and toxicological measurements. Special attention should be given to drugs which are administered by injection or for a prolong period of time. [5]

The technical measurements mentioned above, are to be performed in dedicated facilities for this purpose. Moreover, the principle of "closed systems" between equipment used and physical barriers systems must be applied. A mechanism for dust removal needs to be in place and specialized technologies such as air – locks and pressure cascade should be used to avoid possible airborne contamination. Single use and disposable utensils have to be used when appropriate.[5]

If a product demonstrates high risk of cross – contamination all the necessary protective clothing should be provided and used, the working performance of workers is compelled to be supervised to ensure compliance with procedural controls and training. All the production areas must have a cleaning verification, a measurable waste handling system must be designed, and all spills, accidental events or deviations needs to be recorded. [5]

In a GMP regulated production, validation studies performed in accordance with described procedures reenforce compliance. These validation processes must be conducted periodically.

The suppliers of starting materials need to be selected, qualified, and approved in a documented way and as part of the pharmaceutical quality system, similarly with the purchase and acceptance of the products they are offering. Of course, the level of supervision must be in correlation with the risk present. All the decided quality standards ought to be clearly stated and discussed with the suppliers. Full traceability should be guaranteed. The compliance with GMPs and GDPs is ought to be confirmed through audits performed by the pharmaceutical company and targeted to

manufacturers and distributors. Moving forward, minimum information which starting material labeling should include are relayed. Also, the identity of each container purchased must be measured through specific procedures and only the ones that gets approval by the quality department can be used in the production. The responsibility for these testing falls in the producer of finished materials authority. Finally, only products which are dispensed by designated persons according to the above requirements can be sold.

Prior to any processing procedure of intermediate and bulk products, it must be guaranteed that working areas and equipment about to be used are clean and the absence of any starting material, finished products or finished products residues or documents not essential for the current operation is guaranteed. All the critical processes of this kind should be validated. [5]

All the above-mentioned steps and requirements also apply to packaging materials and special focus is given to printed materials. While packaging, the name and batch numbers of the products must be displayed, and special attention should be given to avoid mix ups and cross – contamination. The quantity, identity and conformity with packaging standards must be inspected upon delivery while checks of the product during packaging should incorporate at the minimum the below:

- The overall appearance of the packages
- If the packages are fully stacked
- Whether the appropriate products and packaging materials are used
- Assure that the over printing is the correct one
- If line monitors are functioning properly [5]

In this point, it is underlined anew that any product which was part of any uncommon event, can only be reintroduced into the production process after an authorized person has inspected, investigated and approved it. Finished products are to be put in quarantine until their final release.

All rejected, recovered, or returned from the market products need to be either destroyed or stored in a dedicated area and reused after it is evident that their quality is sufficient.

Finally, if a manufacturing constraint can potentially lead to out of the ordinary cutbacks in the supply, the manufacturer has the obligation to notify the marketing authorization holder accordingly.

4.1.6 Chapter 6: Quality Control

In general, quality control is a broad field which covers the subjects of sampling, specifications and testing as well as the organization, documentation and release procedures. [6]

It is essential that every authorized manufacturer should maintain a quality department that is independent from the production.

This subsection of part I provides an in-depth analysis on the Good Quality Control Laboratory Practices. It begins by highlighting that personnel, premises and equipment facilitated inside the laboratory should be appropriate for the corresponding task and that the movement of laboratory equipment must be avoided in order to avoid cross contamination.

Regarding documentation, the same principles as the on described in chapter 4 are restated and a list of details which are necessary to be documented are listed, as follows.

- Specifications
- Procedures describing sampling, testing, records, recording and verifying
- Procedures for the calibration and maintenance of equipment
- Procedures for investigating out of specifications and trend results
- Testing reports
- Data from environmental monitoring (if required)
- Validation records (where applicable) [6]

About the sampling process, it is clearly stated that it must be conducted and documented according to previously approved written procedures and that the samples taken should be representative of the batch of materials or products from which they are collected. Also, every package that contains samples have to be labelled accordingly.

Concerning the testing procedure, it is very important that all methods used are validated and the results gathered are recorded (minimum requirements for data included in the records are given) and potential trends are estimated. Moreover, the methods facilitated and according to which all in process controls are performed, must be approved by the quality control department. Also, appropriate reference standards ought to be established according to their intended use. In addition, if the use of animals for testing components, materials or products is required, then, they must be bred, kept, controlled and if necessary quarantined, in a way that guaranteed their suitability for the purpose. [6]

Moving forward, the necessity of a well refined on – going stability program, which will monitor the stability of the final medicinal product and locate potential issues, is highlighted. A detailed and documented procedure must be in place describing the stages of the control throughout the product's lice cycle. It is essential that the number of batches tested, and the frequency of the sampling must guarantee sufficient data for trend analysis. The results of the stabilities studies should be available at any time to key personnel and, in particular, the qualified person and all data generated should be written, maintained and subjected to periodic review while any sign of deviation must be investigated.

At last, if a need for a technical transfer of testing methods arises, first it must be made sure that these methods are in compliance with the ones described in the marketing authorization or the corresponding technical dossier. Also, a detailed protocol should be established for the transfer of testing methods between laboratories.

4.1.7 Chapter 7: Outsourced Activities

In a global and complex pharmaceutical industry, many times, a number of activities often are outsourced. If a GMP regulated activity is outsourced then it must be adequately defined (through a written contract according to marketing authorization and the related regulatory framework), agreed and controlled.

The contract giver should make sure that its quality system is capable of controlling and reviewing the outsourced activities for which he holds the final responsibility. Furthermore, the contract giver is in charge of evaluating the contract acceptor prior starting to outsource tasks. After beginning to collaborate, he has the obligation to make sure that all information and knowledge required in order for the contracted operations to run smoothly are available to the contract acceptor. Also, the contract giver ought to monitor and assess the performance of the contract receiver. [7]

On his end, contract acceptor should be in procession of sufficient premises, equipment, knowledge, experience, and personnel to successfully implement the activities which he has taken upon. In no case is he allowed to subcontract to a third party or perform changes that are not described in clearly in the terms of the contract without having secured prior approval. Also, he oversees ensuring that every material, product or knowledge provided to him are correct and suitable for their intended use. [7]

The contract itself should clarify the corresponding responsibilities and communication paths and the technical aspects of the arrangement must be drafted by a person with sufficient knowledge of the subject. The party responsible for performing each step of the outsourced activity must be clearly defined and all records produced ought to be available to the contract giver at any given time. The later must be granted the authority to perform external audits whenever he sees fit. [7]

4.1.8 Chapter 8: Complaints and Product Recall

Extensive changes were made to this subsection with the greatest being that it is now mandatory for quality risk management principles to be taken into account when investigating quality defects or complaints or decisions about product recalls, corrective and preventative actions are being taken.

All personnel involved with these subjects should not only be adequately trained and have relevant experience but also be independent of the sales and marketing departments. Inter – disciplinary teams can only be composed after careful consideration. [8]

The handling and investigation of complaints and assessment of potential defects must be conducted according to written procedures and all results be documented and evaluated. If a defect is located in the end or even suspected, batches of similar products or even other products needs to be investigated. In addition, trend analysis has to be performed in order to locate reoccurring problems. All decisions taken should be timely and reflecting the level of risk posed. Moreover, during the investigation phase of quality defects, a root cause analysis must be performed.

In the case when a recall action is necessary, it needs to be performed swiftly. In order to achieve this, all batch / product distribution records should contain all required information and be available at any time. If the decision for a recall to be carried out is taken, all concerned competent authorities ought to be promptly informed. Regarding the recalled products, they need to be identified and stored in a separate and secured are to be then disposed or reworked (only after consulting with the supervising authorities). Finally, the recall process as well as other risk reducing actions, such as the issuance of cautionary communications, must be evaluated on a periodic basis. [8]

4.1.9 Chapter 9: Self Inspection

The very essence of Good Manufacturing Practices lays in the belief that by implementing operations proven by experienced and backed by scientific knowledge, consistent quality can be achieved, and the producer has a lot of benefits to yield from this. [9] Having understood this, regular and impartial self-inspections should be carried out in an independent and thorough manner. These audits can be conducted by external experts, or a competent qualified employee of the company and their end goal is to monitor the implementation and overall compliance with GMP principles while proposing required corrective actions when necessary.

Detailed records of the above-mentioned self-inspections must be always kept. During such audits, personnel matters, premises, equipment, documentations, production, quality control, distribution, and the existence of procedures for dealing with complaints and recalls are only some of the subjects that should be examined for compliance with the overall principles of Quality Assurance. [9]

4.2 Part II: Basic Requirements for Active Substances Used as Starting Materials

The second Part of the GMP guidelines focuses on the Active Pharmaceutical Ingredients (APIs). It largely focuses on the same topics as the first part and specifies certain aspects, unique to the active substances, while offering some extra details on some areas.

This Part of the guideline was published in November 2000, originally as Annex 18 to the GMP guide and with final deadline for coming into operation the 1st of September 2014. It basically transforms the generic principles of Good Manufacturing Practices for active substances into a unified and detailed guideline, since the complete revision of several Annexes and of section 1.2, renders Part I insufficient to cover the whole length of APIs production. [10] The objective of this initiative is to ensure the quality and purity of active substances in relation to their specification.

It is important to highlight the fact that these guidelines do not have effect to production steps taken place before the first introduction of the Active Substance Starting Material into the process. As a result, manufacturers need to specify the exact point at which the production of such material begins.

Below, follows a comparison of the content of Part I and Part II (where relevant) and an analysis of the unique elements of the second Part.

4.2.1 Quality Management

In this section, the basic principles of quality management, already discussed in the preview part, are mentioned anew. In addition, the need for an independent quality unit(s), charged with both quality assurance (QA) and quality control (QC) duties is highlighted. Depending on the size and organizational structure of the company, it might be necessary to maintain two separate QA and QC units. Moving on, the guideline deepens further into the unit's responsibilities and covers the areas of Production Activities, Internal Audits / Self – Inspection (special focus is given to this subject) and Product Quality Review (which must be done periodically and consistently). [10]

4.2.2 Personnel

Regarding personnel matters, Part II of the EU guidelines refers to the same subjects as part I since they are relevant for APIs too.

4.2.3 Buildings and Facilities

The basic difference in this subsection can be located in the segmentation that is being used. Part I divides Buildings and Facilities based on the area that they cover while Part II relies on Design and Construction as well as Utilities (e.g., steam, gases, compressed air, heating, ventilation, and air conditioning), Water etc. for the separation. [10]

4.2.4 Process Equipment

The areas of Design and Construction, Equipment Maintenance and Cleaning and Calibration are reexamined here with greater detail. An addition to the subjects previously discussed is the refer to Computerized Systems and more specifically the need for qualification and security while using them.

4.2.5 Documentation and Records

The importance of a well-structured documentation system and the corresponding specifications is underlined here afresh. Moreover, equipment cleaning and use record, records of raw materials and intermediates, API labelling and packaging materials are rediscussed. Moving one step further than Part I, the concept of Master Production Instruction is introduced here for the first time (consisting of Master Production and Control Records), together with Batch Production Records (including Batch Production and Control Records), Laboratory Control Records (all data produced during tests must be recorded in order to guarantee compliance with specification and standards) and finally Batch Production Record Review (highlighting that every deviation,

investigation and out of specification reports must be reviewed before the batch gets approved to be released). [10]

4.2.6 Materials Management

Most of the things analyzed in this subsection have already been scatteredly mentioned in the previous part. More specifically, written procedures must in place for receipt, identification and possible quarantine of incoming materials (special reference is made in the need to avoid cross-contamination in the case when bulk deliveries are taking place in non-dedicated tankers for the purpose) as well as for storage, handling, sampling and testing (in cases of importing production materials from third countries, full analysis must be done on at least three batches before allowing to reduce in-house testing) [10] and of course for the final approval or rejection of the corresponding materials. All the above-mentioned procedures should be periodically re-evaluated.

4.2.7 Production and in – Process Controls

At first, production operations are covered, meaning that the need for raw materials measurement is being established, designated steps in the production process are defined where expected yields must be compared with actual yields and deviation and processing status of crucial equipment should be monitored. Specific time limits need to be set and met while possible deviations should be well recorded and assessed. Steps that can cause variabilities in the overall quality of active pharmaceutical ingredients or used intermediates must be identified, their progress must be monitored, and their performance controlled with in – process sampling and controls. In case when batches of APIs are being blended (meaning that materials sharing similar specification are combined to produce a homogeneous intermediate or API), the new blended batch ought to be properly controlled, documented, and tested for conformance with established specification and traceability. Finally, a full contamination control has to be implemented recurrently. [10]

4.2.8 Packaging and Identification Labelling of APIs and Intermediates

This section, covers the same areas as the ones in Part I, meaning issues related to packaging operations and materials (with their corresponding specifications) as well as to label issuance and control procedures (more specifically the issuance, handling, storing and destroying of labels when needed).

4.2.9 Storage and Distribution

In this point it is emphasized that there should be proper and adequate facilities for the storage of all materials under safe conditions. After the quality unit releases a batch of APIs or intermediates (and only then), sufficient distribution procedures must be in place to guarantee their quality during transit, while making potential recalls possible in a timely manner.

4.2.10 Laboratory Controls

In accordance with the above, the existence of adequate facilities is deemed to be necessary, allowing for the stated specifications to be met. In addition, every sampling or testing process must be documented at the time of performance and backed by sound scientific evidence. Any deviation from defined standards should be investigated and documented. Certificates of Analysis, containing a detailed list of every test conducted, the decline limits and the final results gathered, ought to be provided during the testing of each API or intermediate batch. Moreover, a reoccurring testing scheme for the monitoring of the stability attributes of APIs must be designed and the results yielded should be the guide in determining proper storage conditions and expiring dates. In order for this stability program to be efficient, minimum of one batch of produced API per year should be added to it (more often for products with short shelf-lives) and reserve samples should be kept for potential future quality evaluations. [10]

At this point, it should be mentioned that so far in Part II, the areas covered were similar to the ones in Part I but moving forward from here, Part II deals with separate subjects.

4.2.11 Validation

The need for a written validation policy which will determine the operations that are crucial to ensure the purity and quality of the active pharmaceutical ingredients is highlighted here for the first time. This validation policy must be specified through a validation protocol which will analyze how a particular procedure ought to be performed and specify the type of validation and number of processes runs appropriate while defining the critical steps of the process and setting acceptance limits. In the end, a validation report must be drafted.

Subsequently, the types of qualification (design qualification, installation qualification, operational qualification and performance qualification of critical equipment and ancillary systems) and the different existing approaches to process validation (prospective validation which is the universally preferred method, concurrent validation and retrospective validation) are discussed. [10] Also, it is underlined that the number of processes runs for validation previously mentioned, are inseparably linked to the complexity of the process or the immensity of a proposed differentiation to an existing procedure. During every validation study, special attention must be given to the control and monitoring of critical parameters. If the analytical methods chosen are not part of the relevant pharmacopoeia or any other highly acknowledged standard, they must be validated too with regards to ICH guidelines. Finally, a system that has been validated must be nonetheless reviewed systematically, especially if the risk for contamination or carryover of materials is substantial.

4.2.12 Change Control

Every change which carries the potential to influence the control or production of APIs must be thoroughly evaluated with emphasis on the possible impacts on the quality. The first batches produced after a change is implemented must undergo enhanced testing and evaluation.

4.2.13 Rejection and Re-Use of Materials

If a specific material fails to meet confirmed standards it should be pointed out, put into quarantine if necessary and then rejected in a documented way. A rejected material, besides being discarded, can be handled in two ways and these are through reprocessing (meaning the introduction anew of a non-conforming intermediate or API directly back into the process and reutilize using proper chemical or physical operating steps) or reworking (it is of the greatest importance that reworked batches have gone through strict testing, evaluation and documentation which showcase that the quality of the emended material is not inferior to the original one. [10]

On the other hand, recovery and re-use of materials and solvents (either in the same or in different steps) is possible and acceptable given the fact that certain standards are met, and the recovery processes are well controlled and monitored before re-using or co-mingling solvents with virgin materials. In the case of returned APIs or intermediates, they should be labelled appropriately, quarantined and then they can be either reprocessed, reworked, or destroyed. [10]

4.2.14 Complaints and Recalls

A written procedure must be in place for handling (recording and investigating) all received (both orally and in writing) quality related complaints. Following the investigation of a complaint, a second written procedure should describe the circumstances under which a recall of an API or an intermediate is necessary.

4.2.15 Contract Manufacturers

All contract manufacturers (including laboratories) must operate in compliance with GMP values in order to avoid cross – contamination and to allow traceability. At the same time, every contract manufacturer should be evaluated and work under a signed and approved contract.

4.2.16 Agents, Brokers, Traders, Distributors, Re – packers and Re - labelers

This section is directly applicable to all third parties who are involved in the repacking, relabeling, manipulating in any way, distributing, storing, and getting ahold of an API or intermediate. All the above-mentioned stakeholders should be following GMP principles as described in this guide in order to avoid cross contamination, compromise of quality and purity or loss. More specifically, they should ensure that the traceability of the material is guaranteed and establish an effective quality management system. Moreover, all appropriate stability studies ought to be performed to assign expiration or retest dates. Transfer of information must be facilitated, and all quality and regulatory information received from the manufacturer be transferred to the customers and vice versa. [10] Closing this segment of the guide, it is highlighted that all complaints, recalls and returns should be recorded and handled appropriately.

4.2.17 APIs Manufactured by cell Culture / Fermentation

This subpart is covering the production of APIs or intermediates from cell culture of fermentation. This procedure includes various biological processes like cultivation of cells or extraction and purification of material from living organisms with possible more intermediate stages. The requirements for maintaining a cell bank and keeping all related records are listed, the parameters, equipment and personnel required for cell culture and fermentation are discussed, and harvesting, isolation, purification and viral removal / inactivation steps are relayed. [10]

4.2.18 Viral Removal / Inactivation

In this final section, all viral removal / inactivation steps are analyzed. More precisely, the importance of maintaining stable quality with the help of a quality unit, independent from production and charged with the duty of approving or rejecting every batch, is highlighted anew. Moving forward, the subject of equipment and facilities, control of incoming raw materials and production are examined. It is interesting to note that in this case, expected yields from production can be more varying and less determined than the ones used for commercial purposes. Also, variations investigations are not mandatory. If an API is used for clinical trials, specific features apply since single batches are produced and changes are occurring constantly during development (as knowledge is gained and production is scaling up) and as a result process validation is hard to implement. Clinical trials in many cases cannot be validated by nature prior to testing but this does not mean that solid laboratory controls should not be in place while all methods must be backed up by scientific data. Finally, the importance of documentation is highlighted once again.

Part II ends with a thorough Glossary for all new terms used.

4.3 Part III: GMP Related Documents

Part III of GMP guidelines includes all complementary files which can become useful in the process of implementation.

4.3.1 Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities

This guideline came into effect in 2015 and deals with the cases when a number of different medicinal products are being produced in the same facility and as a result a bigger risk of cross – contamination is present. To address this issue, specific threshold values, based on toxicological data, are determined. This sub section covers the process by which this threshold levels are decided and their importance. A very important index in this direction is the Permitted Daily Exposure (PDE), which represents the daily dosage of a substance that is highly unlikely to cause any harmful health effects. In addition, special consideration is given to active substances with a genotoxic potential (it is considered that any level of exposure poses a great risk) , active substances

with a highly sensitizing potential, therapeutic macromolecules and peptides, investigational medicinal products (phase I and II) and in cases where there is lack of animal data on reproductive and developmental toxicity. [11] Finally, the process through which the PDE is determined (literature review, scientific discussion, and final choice) should be well documented in a determination strategy report.

4.3.2 Internationally Harmonized Requirements for Batch Certification

A batch certification is required under the Mutual Recognition Agreements (MRA), the Agreements on Conformity Assessment and Acceptance of Industrial Products (ACAA) and other arrangements, regarding the GMPs, between the European Union and third countries. This document provides all the necessary requirements for the batch certification. More specifically, a full quantitative and qualitative analysis must be held in order to make sure that the final quality of the products is in compliance with the marketing authorization license. The certificate can also be used for non-finished products, active ingredients, and investigational pharmaceutical products used in clinical trials and it must always be available to regulatory authorities. The last revision made to this guideline when these lines are written were made in 2011. [12]

4.3.3 Template for Investigational Medicinal Products Batch Certificate

This section provides a template for the batch certificate needed for investigational medicinal products. The template follows the information underlined in subsection 3.3.2 and which are relayed below.

1. Name of product
2. Importing country
3. Marketing authorization number or clinical trial authorization number
4. Strength / Potency
5. Dosage form
6. Package size and type
7. Batch number
8. Date of manufacture
9. Expiry date
10. Name, address and authorization number of all manufacturing sites and quality control sites
11. Certificates of GMP compliance of all sites listed under 10 or, if available, EudraGMP reference numbers
12. Results of analysis
13. Comments
14. Certification statement
15. Name and position / tittle of person authorizing the batch release
16. Signature of person authorizing the batch release
17. Date of signature [18]

4.3.4 Explanatory Notes on the Preparation of Site Master File

The necessity of a Site Master File is underlined in chapter 4 of the Good Manufacturing Practices guide. It is issued by the manufacturer and should contain all information regarding the quality management procedures in place. This guideline, offers notes on how to prepare an adequate Site Master File, containing all production operations. In detail, the following information must be included.

1. General information on the manufacturer
    a. Contact information of the manufacturer
    b. Authorized pharmaceutical manufacturing activities of the site
    c. Any other manufacturing activities carried out on the site
2. Quality management system of the manufacturer
    a. Details regarding the quality management system of the manufacturer
    b. Release procedure of finished products
    c. Management of suppliers and contractors
    d. Quality risk management
    e. Product quality reviews
3. Personnel
4. Premises and equipment
5. Documentation
6. Production
    a. Type of products
    b. Process validation
    c. Material management and warehousing
7. Quality control
8. Distribution, complaints, product defects and recalls
9. Self-inspections [13]

4.3.5 Reflection Paper on Good Manufacturing Practice and Marketing Authorization Holders

This paper is focused on Marketing Authorization Holders (MAH) companies, which may or may not be directly involved in the production of the pharmaceutical products but bare a lot of responsibilities non the less.

Marketing Authorization Holders have a unique place in facilitating GMP compliance. More specifically, they deal with the following subjects.

1. They must provide adequate evidence of GMP compliance
2. In some cases, they should prepare a shortened version of the Veterinary Marketing Authorization Dossier
3. They must make sure all labelling and packaging information are correct and available to regulatory authorities
4. Are subjected to all responsibilities stated in chapter 7 of the GMP guidelines
5. They should make certain that all regulatory commitments are met
6. A two-way communication approach must be facilitated with all relevant parties
7. Data integrity needs to be guaranteed

8. A compliance management process has to be in place to ensure that all requirements are fulfilled, otherwise, the marketing authorization can be revoked at any given time [14]

Each GMP requirement is quoted with the exact text that is used in the GMP guideline while references and explanations are provided. In detail, the areas following are covered.

1. Outsourcing and technical agreements (it is noted that only tasks and activities can be delegated to third parties, but the MAH is always accountable for the responsibilities)
2. Audits and qualification activities
3. Communication with manufacturing sites and competent authorities (the need for a two-way communication approach is highlighted anew and specific examples of required communications are given)
4. Product quality reviews
5. Quality defects, complaints and products recalls (a designated contact person should be appointed, and all notification requirements must be met)
6. Maintenance of supply of medicinal products
7. Continual Improvement activities (in accordance with new scientific advances and changes to EU GMP guidelines)
8. Falsified medicines directive (FMD) related responsibilities [14]

4.3.6 ICH Guideline Q9 on Quality Risk Management

As already mentioned, ICH guidelines preceded and vastly incorporated the EU Good Manufacturing Process guidelines. As a result, the Q9 section which is referring to important subject of risk management is included here.

The principles of quality risk management are relayed and then a general process is described, as portrayed in the figure below.

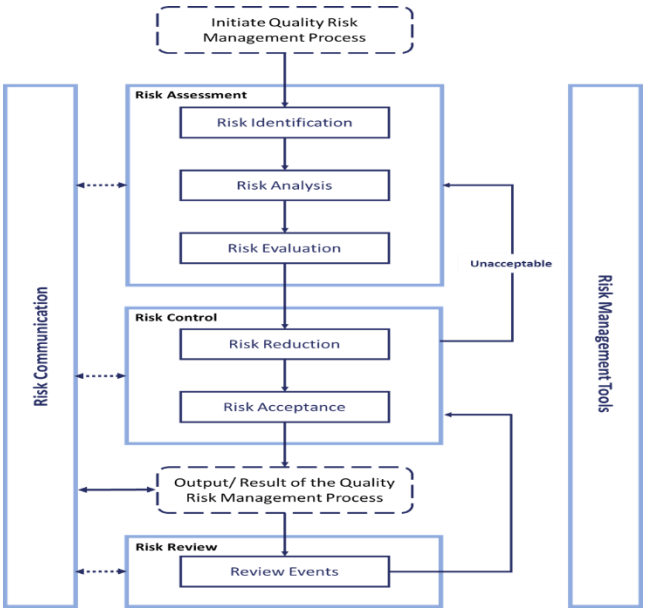

Figure 8: Overview of a typical quality risk management process [16]

Then, the most basic risk management methodologies (they are listed below) are discussed.

1. Basic risk management facilitation methods (flowcharts, check sheets, etc.). These are further analyzed in Annex I, while Annex II relays some examples of potential applications for quality risk management
2. Failure mode effects analysis (FMEA)
3. Failure mode, effects and critically analysis (FMECA)
4. Fault tree analysis (FTA)
5. Hazard analysis and critical control points (HACCP)
6. Hazard operability analysis (HAZOP)
7. Preliminary hazard analysis (PHA)
8. Risk ranking and filtering
9. Supporting statistical tools [16]

4.3.7 ICH Guideline Q10 on Pharmaceutical Quality System

Following Q9, the Q10 guideline regarding the pharmaceutical quality system is also included in Part III. This guideline does not aim to create new requirements but rather assist in the direction of fulfilling the regulatory demands throughout the product's lifecycle.

By implementing the Q10 model, product realization is achieved, a state of control is established and maintained, and continual improvement is facilitated. This can be done by making use of knowledge and quality risk management.

A specific section of Q10 is dedicated to describing the management responsibilities, by dividing them into the areas of management commitment, quality policy, quality planning, resource management, internal communication, management review, management of outsourced activities and purchased materials and management of change in product ownership. [17]

The importance of continual improvements of process performance and product quality is highlighted anew by underlying the significance of setting separate lifecycle goals and of incorporating all pharmaceutical quality system elements.

Finally, the need for achieving continual improvement of the whole pharmaceutical quality system is stated. In order for this to be done, there should be adequate and periodical management review of the pharmaceutical quality system, monitoring of all internals and externals factors capable of impacting the pharmaceutical quality system and study the outcomes of management reviews and monitoring.

4.4 Part IV: Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products

The final part of the EU guidelines is covering the area of advanced therapy medicinal products (ATMPs). Its aim is not to set any restrains on the evolution and usage of new concepts and technologies and thus, while describing some basic requirements, it

underlines that alternative methods can be used by manufacturers if they are able to prove that their approach can achieve the same goals.

To begin with, Part IV deals with products administered to patients under Article 3(7) of Directive 2001/83/EC or so called “hospital exemptions” and clearly states that they too must be produced following equivalent quality standards as the ones applied to the production of advanced therapy medicinal products with a marketing authorization. [19] Then, the importance of the pharmaceutical quality system is highlighted anew.

A risk-based approach must be adopted for the development of ATMPs, but it is acknowledged that since they are often produced in an academic or hospital area, a certain level of flexibility should be allowed because these sites are operating using unique quality systems, different than the ones required under GMPs for the production of conventional medicinal products.

Having said that, the quality and safety of the product must be guaranteed throughout the product lifecycle and starting from the early stages of its development. Nonetheless, as there is a step-by-step increase in the level of knowledge, the intensity of quality assurance endeavors will step up accordingly. As a result, corresponding manufacturing procedures and control methods are expected to gradually become more detailed and thorough as the clinical trials move to more advanced stages.

Moving forward, the subject of personnel is examined with special attention to the person responsible for quality control and the qualified person. Regarding the premises used, the classification of clean rooms and clear air devices according to ISO 14644-1 is introduced. More specifically, four grades (A, B, C and D) are defined and specific concentration limits for airborne particles (in order to ensure an aseptic environment in the clean room and monitor contamination risk for isolators and biosafety cabinets), microbial load and specific microorganisms (such as yeast) are set (both at rest and in operation). [19]

Then, Part IV, covers the area of equipment used, further deepen in detail specific for the ATMPs. The documentation subject is also studied and is stated that the level of specification and instructions must be relevant to the type of product and stage of development. Proper and thorough documentation should be in place to ensure that the unique characteristics of each batch can be identified despite the evolution – refinement process. A product failed to meet the characterization requirements is prone to potential rejection of the clinical trial results and denial of a marketing authorization.

As it is evident, starting, and raw materials are particularly important for the development of ATMPs and when possible, the materials used should be in accordance with the Ph. Eur 5.2.12 (general chapter on raw materials of biological origin for the production of cell based and gene therapy medicinal products) and also, raw materials must be of pharmaceutical grade, with the exception of instances when only research grade raw materials are available. At the same time, a mechanism for assessing the contamination risk across the whole supply chain have to be in place, paying special attention to microbial safety and Transmissible Spongiform Encephalopathy (TSE). [19]

Another important parameter is the quality of the starting materials and especially cells and human tissues which must be in compliance with the donation, procurement and testing standards of the Directive 2004/23/EC or if appropriate Directive 2002/98/EC. The risk of transmitting both known and unknown pathogens (including potential new infectious diseases) to human is escalating greatly when xenogeneic cells or tissues are used. As a result, a need for a firm control of donor animals to ensure that they are healthy and raised in pathogen free (SPF) conditions (monitored captivity) must be designed. Every ill-health occurrence has to be investigated and dealt with. For allogeneic products that a match between the donor and the patient is not mandatory, the use of master and working seed lots/cell banks is recommended but not imposed. [19]

Special attention is given to the production process, covering the areas of general principles, handling of incoming materials and products, utilities (water, medical gasses, and clean steam), prevention of cross contamination and aseptic manufacturing. For the later, details for the aseptic processing validations are given, stating that it should incorporate a simulation test using a sterile microbiological growth medium and / or placebo.

Moreover, it is highly likely that packaging activities of ATMPs will present increased levels of complexity and liability to errors, which may also be more difficult to locate in cases where blinded products with the same layout are used. In addition, the blinding system used must be carefully described in the Product Specification File and if the manufacturer is responsible for generating randomized codes, special actions should be taken to ensure that all blinding information can be fast available to authorized investigators before delivery while securing personal data from accidental unblinding.

The subjects of finished, rejected, recovered, and returned materials are also discussed covering the same areas as the previous parts.

Part IV provides great details about qualification and validation. More specifically, the steps of qualification process are relayed which are the ones following.

1. Setting the user requirement specifications
2. Design qualification
3. Verifying compliance with the user requirement specification (installation qualification, operational qualification, and performance qualification)
4. Documentation [19]

In regard to validation, cleaning validation, process validation (even though the production process of investigational ATMPs is not mandatory to be validated, all necessary actions should be taken to guarantee compliance with the standards set in the clinical trial authorization), validation of test methods and validation of transport conditions are examined.

Then, the role of the qualified person is further described, and it is underlined that, besides the requirements laid out in Article 49 of Directive 2001/83, QPs in charge of ATMPs must also have proper training and previous experience in the unique attributes of these items, cell and tissue biology, biotechnological techniques, cell processing, characterization and potency testing. [19]

For a batch to be released, the following three steps should be followed.

1. Checking that the production and testing of the batch has been done in compliance with corresponding requirements
2. Certification of the finished product batch made by the qualified person
3. Final assign of the release status to the batch [19]

Beside the above, there are some cases when, because of the short shelf life of the ATMP, it may need to be released prior to completion of all quality control steps. To counteract this, part IV allows for a batch certification procedure which will take place in various stages.

Another issue is that the ATMPs may be necessary to manufactured in close proximity to the patient for various reasons. In cases like this, a decentralized approach is used where multiple sites across the EU are oversighted by a central hub. [19]

Subsequently, details are given for the handling of undesigned deviations and for the administration of out of specification products.

Furthermore, the vast topic of quality control is covered, focusing on sampling, testing and the establishment of an on – going stability program. The different types of samples that need to be maintained are the ones listed here.

- Samples of raw materials
- Samples of the starting materials
- Samples of active substances and intermediate products
- Samples of primary packaging materials
- Sample of fully packaged unit (retention sample) [19]

Then, the obligation of both the contract giver and the contract acceptor as part of an outsourced activities arrangement are discussed.

As long as quality defects and product recalls are considered, and when a blinding procedure is required, it must be made sure that the rapid unblinding of products if the need arise for a prompt recall is guaranteed but in a manner that the identity of the blinded product is disclosed only if absolutely necessary.

The next subsection of part IV is dealing with the genetically modified organisms which may pose a threat to the environment when disposed and highlights the need for a risk assessment that will lead to a categorization of the products as negligible, low, moderate, or high risk for the environment. Also, it is underlined that this section is without prejudice to the requirements that may be applicable to investigational ATMPs under Directive 2001/18/EC (Directive of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC) and Directive 2009/41/EC. [19]

The penultimate subsection of this part examines the reconstitution of products after their release. The term reconstitution refers to each and every activity which takes place between batch release and final administration to the patient and are not considered to be a manufacturing step. As it is easily understood, if an activity leads to considerable

manipulation of the ATMP, it cannot be considered reconstitution (a number of examples are given). [19]

Finally, all necessary requirements for the automated production of ATMPs is discussed.

4.5 Annexes

Even though most of the subjects related to Good Manufacturing Practices are covered in the 4 corresponding parts, there are still areas which calls for greater details and a more in-depth analysis. This is achieved through the issuance of annexes that provide necessary clarification in specific sections of GMPs.

- Annex 1: Manufacture of Sterile Medicinal Products [20]
- Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use [21]
- Annex 3: Manufacture of Radiopharmaceuticals [22]
- Annex 4: Manufacture of Veterinary Medicinal Products Other Than Immunological Veterinary Medicinal Products [23]
- Annex 5: Manufacture of Immunological Veterinary Medicinal Products [24]
- Annex 6: Manufacture of Medicinal Gases [25]
- Annex 7: Manufacture of Herbal Medicinal Products [26]
- Annex 8: Sampling of Starting and Packaging Materials [27]
- Annex 9: Manufacture of Liquids, Creams and Ointments [28]
- Annex 10: Manufacture of Pressurized Metered Dose Aerosol Preparations for Inhalation [29]
- Annex 11: Computerized Systems [30]
- Annex 12: Use of Ionising Radiation in the Manufacture of Medicinal Products [31]
- Annex 13: The Rules Governing Medicinal Products in the European Union [32]
- Annex 14: Manufacture of Medicinal Products Derived from Human Blood or Plasma [33]
- Annex 15: Qualification and Validation [34]
- Annex 16: Certification by a Qualified Person and Batch Release [35]
- Annex 17: Real Time Release Testing and Parametric Release [36]
- Annex 19: Reference and Retention Samples [37]
- Annex 21: Importation of Medicinal Products [38]

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Section 5. Process Validation

5.1 Introduction

The term validation derives from the world "valid" or "validity" which in turn means "officially acceptable" [3]. It is a concept wildly adopted in the pharmaceutical industry that was first introduced during the 1970s by two FDA's officials, Ted Byers, and Bud Loftus. The idea behind this was to enhance the quality of pharmaceutical products by making sure, in a documented manner, that a desired result with predetermined compliance is assured.

Since then, the concept of validation has expanded to include a wide range of subjects, such as equipment used, analytical methods utilized during quality control, materials, processes, computerized systems, labeling etc. and the list grows constantly. [16]

Validation is a broad approach, spreading throughout the product's life cycle and maintaining the quality alongside. In general, every step of a procedure is verified and consequently the whole process is validated. In this sense, quality is designed and built in the system and thus functionality, consistency and repeatability are confirmed [14]. As it is evident, validation is a cross discipline effort, incorporating people from every level of the organization.

This new approach regarding validation is built upon the principles of Quality by Design (QbD) and Quality Risk Management (QRM) and emphasize the need of deep process understanding and quality orientation from the product's design face up to its commercially production. As a result, process validation is viewed as a consistent proof of quality and reliability rather than a static picture of control. This is made possible by proactively identifying potential quality issues, using a scientific and practical approach to decision making, based on risk evaluation of critical factors [7].

5.2 Definitions

A validated process is a process which is assured in a documented way that will perform within strictly designed and defined criteria. As a result, a high degree of assurance that the manufactured product will meet its predetermined standards and quality features in a continuous and reproductible way is achieved [11].

Consequently, it is considered a key factor in assuring the identity, purity, safety, efficacy and maintaining the quality of the final product [11]. Even though validation has gradually become one of the most important, frequently discussed and acknowledged topics throughout the pharmaceutical industry, there is still no universal approach on the subject and different regulation bodies have introduced separate, non-mandatory guidelines and definitions for this term. The most important of these definitions, are the ones following.

European Commission: Validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes [5].

United States Food and Drug Administration: Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation involves a series of activities taking place over the lifecycle of the product and process [21].

ICH: Process validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality [12].

World Health Organization: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to expected result [12].

5.3 Legislation

As mentioned above, there is no universal approach regarding the process validation, and it is best viewed as an important and integral part of current Good Manufacturing Practices.

More specifically, process validation is established by parts 210 and 211 of the cGMP regulations, both in general and specific terms [14]. In addition, process validation regarding the production of finished pharmaceuticals and components is a mandatory and legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351 (a)(2)(B)) [21].

The guidelines published by the EMA clearly state that the validation must always be executed in total compliance with GMPs, and all data used, produced or collected should be properly stored at the manufacturing site and be available for inspection upon request. At the same time, the validation ought to be carried out in accordance with a validation scheme which should be included in the marketing authorization dossier. The scheme must incorporate a detailed description of the manufacturing process, the tests to be performed and their acceptance criteria and finally an outline of all the extra controls in place. The choice of this particular process validation scheme has to be properly justified. Moreover, in some specific cases (for example when the final product is a biological / biotech product or when a non-standard manufacturing process is proposed), it could be considered necessary to provide production scale validation data in the marketing authorization dossier (number of batches need to be proportional to the complexity of the process or product, the knowledge gained during development, any supportive data at commercial scale, during technology transfer and the overall experience of the manufacturer. [5]

Until recently, if not otherwise justified, a minimum of three production scale batches should be submitted. Lately, both the EU and US approach on process validation have been altered through the introduction of Quality Risk Management and Quality by Design concepts and the prior approach of consecutive validation runs has been replaced by a more scientific and risk-based perspective [7].

5.4 The Importance of Validation

Validation is one of the most crucial elements in the path of achieving and maintaining quality of the final product. By carefully designing, validating, executing, and documenting each step of the production, the quality of the final product is achieved consistently.

All the above are especially important for the pharmaceutical industry because it uses expensive materials, sophisticated equipment and facilities and highly qualified personnel. It is evident that these resources must be used efficiently in order to avoid the high costs of failures, rejects, reworks, complaints and recalls [11]. After all, it would not be efficient to use equipment not knowing it will meet specifications or employ people not able to perform as expected. [12]

There are three primary reasons for a pharmaceutical company to seek validation (quality assurance, cost reduction and regulation compliance) but many more benefits to yield. An attempt to summarize the benefits of performing validation is relayed here:

- Consistent quality of the final product (reduce batch to batch variation)
- Reduction in complaints, rejection, reworks, recalls and their corresponding costs (cost of quality and cost of noncompliance). Avoidance of unnecessary capital expenditures
- Prompt installation of new equipment and easier maintenance there after
- Faster and more accurate root cause analysis regarding deviations
- Boosts process awareness
- Easier scale up from design phase
- Encourage automations [11]
- Expands real time monitoring and adjusting of process and reduces testing in finished goods
- Enhanced data capabilities, statistical performance evaluation and the ability to set control parameters and limits leads to process optimization and increased confidence about process reproducibility and quality
- Better reporting capabilities
- Improved safety [12]
- Increased output [14]

5.5 Reasons to Validate and Who is Responsible

The importance of validation has been well established by know but it is also crucial to specify the circumstances under which the need for validation arise. These include, but are not limited to, changes into new or existing products such as the ones following:

- Change in site of manufacturing
- Change in batch size
- Change in manufacturing process of existing products or totally new process (e.g., mixing time, drying temperatures and batch size) [11]
- Change in composition or components
- Change in the critical control parameters

- Change in vendor of API or critical excipient
- Abnormal trends in quality parameters
- Out of trend specifications in consecutive batches [12]
- Change in specifications of input raw materials (physical properties such as density, viscosity, particle size distribution and moisture etc.) [11]
- Change in supporting systems
- Change in equipment / system or introducing new ones [e.g. addition of automatic detection system)
- Change in packaging materials (primary container or closure system) [3]
- Cases when the quality control on the final product is poor and thus they are not considered sufficient indicator [19]
- Change in quality parameters of product during Annual Product Review (APR) [14]

So, validation can either be about new activities or items or revalidating existing ones. Revalidation can be divided into periodic / scheduled or after change / modifications.

At the same time, since validation is carried out by designated personnel, it is very important that they are properly qualified for the task and that their responsibilities are properly defined. The validation, cross department, team is in charge of defining the process, coordinating and approving the entire effort (including all of the generated documentation) [12]. The table below shows the person involved in the validation process and their corresponding duties.

Designees	Responsibility
Third Level of Process Engineer	Prepare and review the validation protocol (Title, Market, Batch Size, Report no, Batch Details, Product Details, Reference Documents).
Second Level of Process Engineer	Execute process validation batch. Protect the information concerning reason for validation, product specification and receiving criteria, measuring device used, batch production details, in-process characteristics, validation data, results and conclusions
First Level of Process Engineer	Review validation protocol and clarify the validation report. Ensure that batches according to the plan and approved protocol. Prepare periodic revalidation calendar
Second Level of Quality Assurance Manager	Control of withdrawing sample as explained in the validation protocol. Analyze the sample and confirm validation report.
Head (Engineering)	Analyze the area and equipment
Operation Manager	Analyze and safeguard that the information concerning batch details, finished products details, pack details of input materials, equipment used, batch fabrication details, in-process characteristics, yield monitoring result and conclusion
Authorized Regulatory Person	Analyze batch details, product details, pack details of input materials and certify the validation report
Head (Quality Assurance)	Accept the validation agreement for application and attest the validation report

Table 2: key Responsibilities of Designees Involved in Various Phases of the Validation Process [11], [12]

Another way of separating responsibilities is by dividing and assigning them into different departments as shown below.

Department	Responsibilities
Site Validation	Develop site master validation plan
Manufacturing	Prepares the batches as routine batches for collection of data
Quality Assurance	Ensures compliance, documentation and procedures are in place. Approves protocols and reports. Review validation documents for process approval
Quality Control	Perform validation testing and reviews protocol and report
Research & Development	Deals with product design, installation, and quality. Certify plant, facilities, equipment, and support systems

Table 3: Key Responsibilities of Departments Involved in Various Phases of the Validation Process [11], [18]

5.6 Requirements and Validation Strategy

Knowledge regarding the final product and its production process are key to a successful validation. Through this deep understanding of product development, it is possible to establish sufficient control which in turn will lead to the desired quality attributes.

It is very important that manufacturers:

- Understand the sources of potential variations
- Detect the presence and degree of variations in time
- Be aware of the impact a variation may have on the process in general and on product features in specific
- Control each variation in a way corresponding to the risk it poses [21]

At the same time, detailed pre-established protocols must be in place to guide all actions and properly trained and qualified personnel must be assigned to perform each task. Proper facilities, equipment, instruments, and methodologies should be available. Also, all data generated ought to be reviewed, certified, and documented [12].

Prior to commercial distribution, the producer must reflect on whether he has acquired sufficient understanding and can guarantee high levels of assurance regarding the quality of the final product. A common mistake manufacturer tends to make is focusing their efforts on getting formal qualifications without realizing the importance of understanding the manufacturing process itself and the quality issues which could derive from possible variations. It is also important to make sure that the validation will not be seen as a one-off event. In contrary, the state of control achieved must be maintained even when materials, equipment, environment, personnel, and procedures change [21]. This can be made possible by incorporating a lifecycle approach which will link product development with production and commercial distribution and will cover every manufacturing site while providing adequate data at the same time [5].

To achieve all the above, a carefully studied but also simple and straight forward validation strategy must be developed, paying attention to 5 key points:

- Raw materials from different lots must be used
- Validation batches should be run in succession, in different days and shifts
- The equipment and facilities destined for commercial production must be used during validation phase
- Critical process parameters should be set and limited within operational boundaries
- If the validation protocol requirements are not met, requalification and revalidation are in order [11]

As already mentioned, validation is a continuous and ever evolving process. Evidence of validation should be seen at the corporate level and be reflected in the management structure.

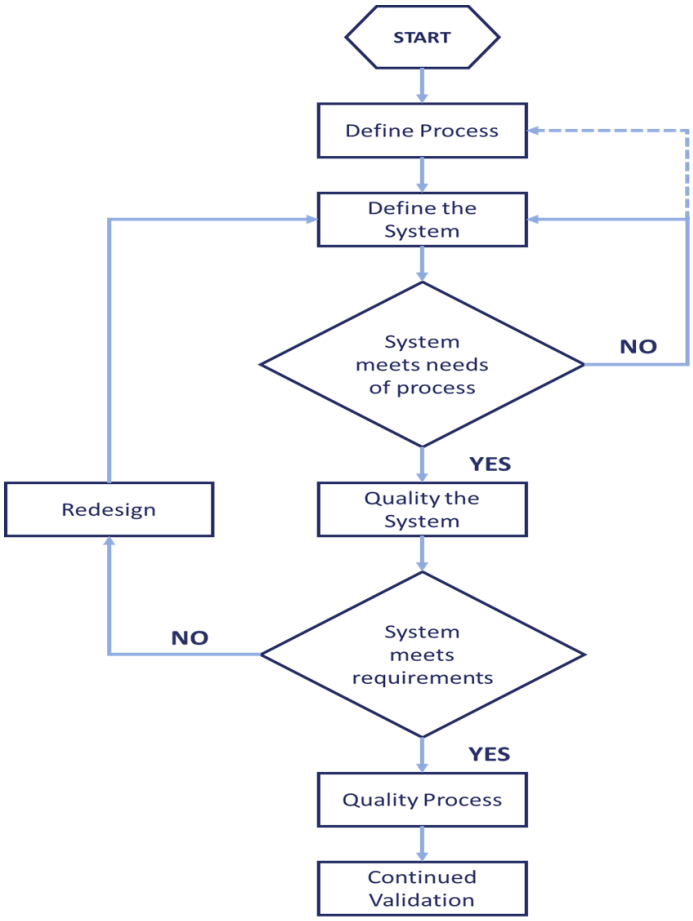

Figure 9: Validation Strategy Flow Chart [11]

5.7 Phases of Validation

The validation is a broad term which cover a wide range of activities. Many different items or procedures can be validated but every validation can be primarily broken down to three distinctive phases.

Phase 1: Pre-Validation or Qualification Phase

All activities related to research and development, formulation, pilot batches, scale up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage, and handling of in-process and finished dosage forms are carefully examined in this first phase as well as equipment qualification, installation qualification, operational qualification, process capacity and master production document [14].

Phase 2: Process Validation

It is verified that established limits of critical parameters are solid and will lead to accepted product even under extreme conditions.

Phase 3: Validation Maintenance Phase

This phase requires the periodic review of related documents (including validation and audit reports) to make sure that no alterations, deviations, failures, or modifications have occurred and that all standard operating procedures are followed [12]. At this stage, an interdepartmental validation team, ensures that there has been no need for requalification or revalidation [14].

5.8 Types of Validation

In this sub section of the chapter, the most important types of validation are going to be further analyzed. It is important to mention that the bare minimum that should be validated are the cleaning procedures, analytical testing, and process (including equipment) [19].

5.8.1 Analytical Validation

For the quality of the product to be verified and in order to ensure that it is maintained throughout the product's lifestyle [14].

Proper testing is established to make sure that no compromise has taken place in terms of the below key parameters:

- **Accuracy:** the proximity between the theoretical true value and the observed one
- **Precision:** The exactness of the analytical procedure. It consists of three levels:
    - **Repeatability:** The exactness under similar conditions
    - **Intermediate precision:** The exactness of tests performed inside the same laboratory but in distinct days, by different analysts and on distinct equipment
    - **Reproducibility:** The exactness between different laboratories
- **Ruggedness:** The degree of reproducibility under different conditions
- **Detection limits:** Lowest quantity of an analyte which may be detected
- **Quantitation limits:** The least quantity of an analyte which can be quantified with exactness and precision
- **Linearity:** The ability of a method to produce results directly related to the concentration of an analyte

- **Range:** The interval between maximum and minimum volume of analyte in a sample
- **Specificity:** The capability to unequivocally assess the analyte of interest
- **Robustness:** The degree of capacity of the method to remain the same after changes in the technique parameters (such as pH, temperature etc.) [16]

Every analytical method which is used in clinical samples examination is necessary to be validated. Analytical validation is the, accepted by laboratory studies, procedure which guarantees that the characteristics of the method used fits the scientific requirements of its intended application. Analytical validation is an essential but time-consuming project for most laboratories [12].

Analytical validation is crucial because it ensures that a new or altered procedure will provide predictable and dependable results, even if performed by different personnel, using comparable instruments, inside similar or totally distinctive laboratories.

There are five steps which are normally followed in order to validate an analytical method:

- System Qualification
- Sampling
- Sample Preparation
- Data Assessment [16]

5.8.2 Cleaning Validation

Cleaning validation is a documented way of achieving high degree of confidence that an equipment (or part of an equipment) or system is effectively and consistently cleaned of residues below a predetermined acceptable limit. Examples of such residues may be, but not limited to, lubricants, airborne substitutes, product residues, microbes etc. [3]. As a result, cleaning validation is key to preventing cross contamination and it includes the development of practical, achievable, and justifiable acceptance criteria, detection limits and sampling methods.

The main reasons for validating the cleaning procedures include:

- Ensuring the safety and purity of the final product
- Preventing contamination
- Satisfying regulatory requirements
- Satisfying customer requests [16]

5.8.3 Computer System Validation

Computer System Validation (CSV) provides documented evidence that a computer system performs the tasks which was designed to handle and produce information and data in an effective and efficient manner as per pre-defined requirements. If CSV is done right the accuracy, consistency, reliability of the system is assured.

Computer System Validation in the pharmaceutical industry is primarily focused on software validation, which is part of the CSV (every computerized system includes some kind of software).

During a typical Computer System Validation procedure, an organization phases some common challenges, as described below:

- **Standards:** Various standards, policies, SOPs, instructions etc. exist across departments and are potentially overlying or even being incompatible, increasing costs and complexity of validation
- **Interpretation:** Extensive debates over the essence of standards and requirements greatly increase costs and time needed
- **Organization and Governance:** Decentralized governance and unclear roles, responsibilities and activities ownerships create additional obstacles
- **Efficiency Across Sites and Departments:** In many cases, multiple validation packages are developed for the same system in different sites or by different departments due to lack of communication
- **Execution:** All the above-mentioned challenges, combined with potentially unqualified individual employees, often leads to excessive rework
- **Tools:** They are employed to reduce the risk of personnel taking shortcuts or skipping steps but can be inflexible and lead to unnecessary efforts
- **Training:** The short training usually provided is rarely sufficient
- **Personnel:** Many pharmaceutical companies employ very capable central validation teams but lack in competent decentralized execution parties [17]

There are five key steps in the Computer System Validation process and are relayed:

- **Validation Master Plan:** A thorough blueprint of the validation process is drawn up in this step
- **Project Plan:** Each step must be performed based on Standard Operating Procedures and the Validation Master Plan
- **Installation Qualification (IQ):** Deeply analyze the installation of new components while setting appropriate checks
- **Operational Qualification (OQ):** Ensures the security (software and physical) and proper operational function
- **Performance Qualification (PQ):** Tests specific applications and overall performance [17]

The importance of Computer System Validation is widely acknowledged across the pharmaceutical industry and the regulatory bodies. This has led the FDA to issue five basic requirements which must be met for systems used in medical devices. More specifically, it is critical that the below are guaranteed.

- Information Security
- Information Backup
- Information Restoration
- Information Recovery in “Disaster” Cases
- Periodic Maintenance [17]

5.8.4 Equipment Validation

The equipment validation is an integral part of validation and is more commonly known as qualification [14]. Equipment plays a key role in production of pharmaceutical products and thus it is very important to validate them prior to using them. The qualification scheme is based on the idea that every equipment should be first designed, then constructed, next maintained and finally adapt to perform the tasks which is designated to operate [3].

Equipment validation can be divided into, the Design Qualification (DQ), the Installation Qualification (IQ), the Operational Qualification (OQ) and the Performance Qualification (PQ).

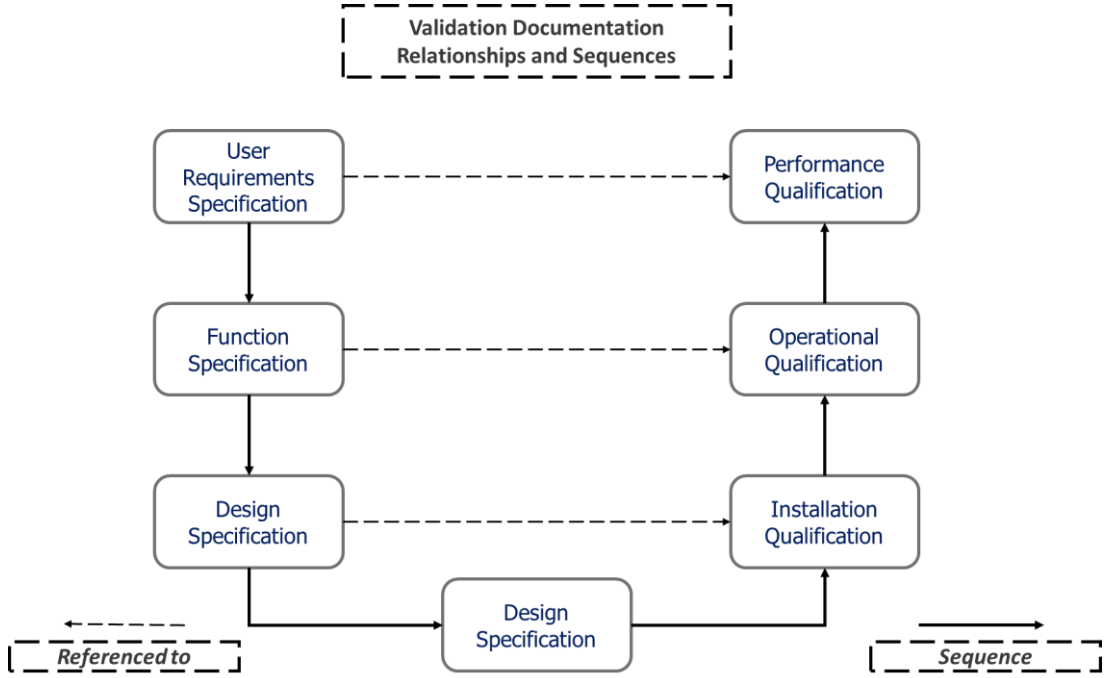

Figure 10: Equipment Validation Process

In most cases, when a need for a new equipment (or change in an existing one) arises, the procurement typically starts by specifying the required documentation, User Requirement Specification (URS), followed by Functional Specification (FS) and Design Specification. Then the qualification begins with the Design Qualification and Installation Qualification (in the pre-validation phase), continuous with Operational Qualification and Performance Qualification (in the validation phase) and finally remain in control through the validation maintenance phase [3].

The above-mentioned validation elements are further analyzed below.

User Requirement Specification (URS): It summarize the requirements and expectations the customer or the user has of the equipment. It covers the areas of:

- Size of equipment and the space it occupies
- Its effectiveness and durability
- The working speed
- Limits of air and noise pollution

- Spare parts availability and after sales services
- Overall construction quality [3]

Design Qualification (DQ): Is the action of making sure that the proposed layout of equipment (or system) will satisfy the URS, FS, will comply with regulatory framework and will highlight the rationale of choosing a specific supplier. It is a very important step and special attention should be given because the impact it will have on IQ, OQ and PQ is significant [12].

Installation Qualification (IQ): Is the action of offering objective evidence that all the key and ancillary features of the equipment are installed (or modified) following manufacturer's layout and dealer's recommendations [14]. Part of IQ can also be considered the Safety Qualification (SQ) which validate that all the safety necessities have been followed [14]. At the same time, it must be established in great confidence that the equipment will operate consistently within pre-defined limits and tolerance [11]. Details of supplier and manufacturer of the equipment together with details (such as the name, color, model, serial number, date of installation or calibration) should be well documented in this step [3].

Operational Qualification (OQ): It consists of several carefully designed tests which can estimate with precision the performance capacity of the equipment and can verify that it this performance is maintained throughout the anticipated operating ranges. In that sense, OQ focuses on a specific piece of equipment rather than exploring performance capabilities of a single product [12].

The OQ is conducted in two stages. Firstly, the Component Operational Qualification in which calibration is a key aspect. Then, System Operational Qualification where it is determined if the entire system operates properly and as a unified whole [18].

The finalized approved operations which arose after functions testing, the approved calibrations, the test results regarding system stability and the various applications of SOPs must be included in the OQ's documentation [3].

Performance Qualification (PQ): Is documented evidence that the equipment installed operates as intended. In this stage, this is insured under actual operating conditions and environmental factors [11]. In other words, it is here proved that equipment can accomplish the requirements set in the DQ phase in a repeatable manner which always meet predetermined quality [12].

The documentation of PQ should at least include the Performance Qualification report, the process stability testing reports (derived from long term productivity data), the acceptance of the product record (based on customer reviews), a register of the actual product and process parameters and a record of routinely performed test results [3].

Re – Qualification (RQ) and Maintenance: While the equipment is getting old or if a need for a change or relocation arises, re – qualification is in order [14]. Changes with no significant impact on in-process or final product quality should be handled via the preventive maintenance procedure [12]. During maintenance, it is important to maintain routine service records, a list of all authorized service engineers and an inventory of maintenance contacts details [3].

5.8.5 Gases Validation

One of the materials which is highly utilized in the manufacturing procedure of the pharmaceutical products are various types of gases. Some examples are carbon dioxide, compressed air, nitrogen gas etc.

Gases can impact the quality of the final product by coming into impact with it (direct impact) or by indirectly affecting it. As a result, a validation plan should be in place to insure that the gas system operates under control.

There are three steps need to be followed in order for a gas system to be validated.

Step 1: Supply of gas of desired purity and in adequate quantity. Special attention should be given to pressure requirements while using the gas at maximum rates

Step 2: Making sure that proper, non-reactive materials are used to construct gas storage facilities

Step 3: Ensure that the distribution system is also made of non-reactive and durable materials and of adequate size [14]

5.8.6 Process Validation

Process Validation is the documented plan which can bestow great levels of confidence that the validated process will always produce a product according to its pre-established specifications and quality features [12]. FDA recommends and integrated team approach to process validation, combining expertise from a variety of departments and disciplines [21].

There are four different types of process validation.

Prospective Process Validation: This type of validation is the registered proof that the process does what is supposed to do based on a pre-defined protocol. It usually takes place prior to distribution of a new product or product made after process revision and should be performed on at least three consecutive production batches [11].

Retrospective Process Validation: In this case, the evidence of process reliability is given after analysis and evaluation of historical data. The aim is to demonstrate that the process has always remained under control [12]. These data derive from production, Quality Assurance (QA) and Quality Control (QC) records. It must be emphasized that retrospective validation can only be accepted when a process is well established, and no change have been made to it in the recent past regarding product's composition, equipment, or operating procedures. A minimum of ten to thirty past consecutive batches should be examined (fewer batches can be examined if this can be properly and scientifically justified) [11].

Concurrent Process Validation: This approach is very similar to Retrospective Process Validation with one key difference. The product produced during the qualification runs will be sold by the pharmaceutical company to the general public at its market price. Because the product may end up to the final customer, the decision to carry out Concurrent Process Validation, must be properly justified, documented, and approved by authorized and competent personnel [11]. It is characteristic that FDA in its guideline underlines that concurrent release of batches is expected to happen rarely

[21]. All critical steps should be monitored, and appropriate production testing must be conducted when some alteration in equipment, formulation or site location have happened [12].

Revalidations: When there is a change in batch size, or some sequential batches don't produce products according to process specifications revalidation (repetition of validation) is required to verify that these changes do not impose adverse effects on the features and quality of the product. The documentation required remains the same as the one in the initial validation which has been made [12].

The assessment of data necessary for the Process Validation requires a set of activities which are taking place throughout the product and process life cycle. This sequence of tasks can be divided into three stages.

Stage 1 – Process Design: Process Design is the action of defining the commercial manufacturing process suitable for commercial manufacturing [21]. In this stage, all knowledge and experimental data which will be the basis for next stages are generated. Process Design, if done right, can offer great process understanding and can locate possible sources of variability. Development formulation, scale up studies, transfer of technology, storage and handling of the in-process and finished products, Equipment Qualifications, Master Production Documents, and process capabilities are some of the concepts concerning this stage. The acceptance of strategy for the process control happens in this step [12].

Prior knowledge of similar processes, combined with the principles of risk management, can be used to identify a list of potential Critical Quality Attributes (CQAs) and the parameters which can potentially impact them (and rank them accordingly). CQAs are the physical, chemical, biological or microbiological properties or features which must be inside preset limits, range, or distribution to ensure the desired quality [7].

Based on these evaluations, the necessary experiments are prioritized, and a list of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) is drawn.

- **Process Scale up:** The term scale up may refer to either increasing the batch size or the procedure of applying the same process to different volumes. First, a risk assessment should be carried out and based on that, the best strategy for scale up to pilot or industrial batch is decided [7]. Proper information, gathered through development and process optimization studies, is key to avoiding lengthy and costly tests and justifying that scale up poses no risk to quality [5].
- **Design Space:** After identifying critical parameters and analyzing preliminary experiments, a model is created to define a design space (usually during laboratory or pilot scale) inside which the commercial process is usually performed and validated, in a specific area defined as the Normal Operating Range (NOR) [5]. According to ICH 8, working within the Design Space is not consider a change (moving from one area to another may represent higher or unknown risks though) while movement outside of the Design Space it is, and further Design Space Verification may be needed. The Design Space is

proposed by the producer but still remains subject to regulatory inspection and approval [7].

Stage 2 – Process Qualification: During this stage, the design process is put under judgment in order to make sure that the process is capable of reproducing commercial manufacturing. It is important to mentioned that all GMP procedures should be observed during this stage and that any commercial distribution of the product cannot begin prior to completion of this step [12].

Another goal of this stage is to ensure that all risks, identified in the risk analysis, are under control and all suitable actions are in place [7].

This stage includes two key elements. Firstly, the design of the facilities and qualification of equipment and utilities (as described above) and secondly the Process Performance Qualification (PPQ). The PPQ combines the actual facilities, utilities, and equipment (now qualified) and the appropriately trained personnel to run the commercial manufacturing process, control procedures and components to produce commercial batches. A successfully caried out PPQ will provide the final confirmation of Process Design and that the commercial manufacturing process performs as expected and is able to produce products with required quality even under extreme conditions [21].

Stage 3 – Continuous Process Verification: Is the action of providing continuous assurance that the production procedure remains under a state of control through the entire life cycle. A recurrent check of process related documents and validation audit reports is necessary to ensure that no changes, deviations, or failures have occurred [12]. A wide range of parameters (e.g., process trends, incoming components quality etc.) should be brought under a control and periodically reviewed from this point afterwards [7].

Continuous Process Verification has been introduced as an alternative to traditional process validation and suggest a continuous monitoring and evaluation of process performance. It can be used instead of or in addition to traditional approach. To enable the continuous alternative, pharmaceutical companies should utilize all necessary in-line, on-line or at-line controls and monitor the quality of each batch, keeping an archive of all relevant data [5].

Continuous Process Verification is considered the most suitable tool for validating continuous processes and the responsibility of defining the stage at which the process is considered to be under control lies with the applicant. At the same time, it is a very versatile method that can be introduced at any time in the life cycle of the product and can be used to perform the initial validation as well as to re-validate or even to support continuous improvement [5].

Traditional Process Validation: Is usually conducted after scaling up (or at a pilot batch representing at least 10% of production scale batch) but prior to marketing of the final product [5]. Usually, a minimum of three consecutive batches with the same size as the commercial one is required to establish reproducibility [7].

Hybrid Approach: There might be some cases where the use of both the traditional and the continuous approach is needed for different steps of the manufacturing procedure [7]. The choice of each method should be appropriately justified and clearly stated in the dossier which step is conducted with which approach.

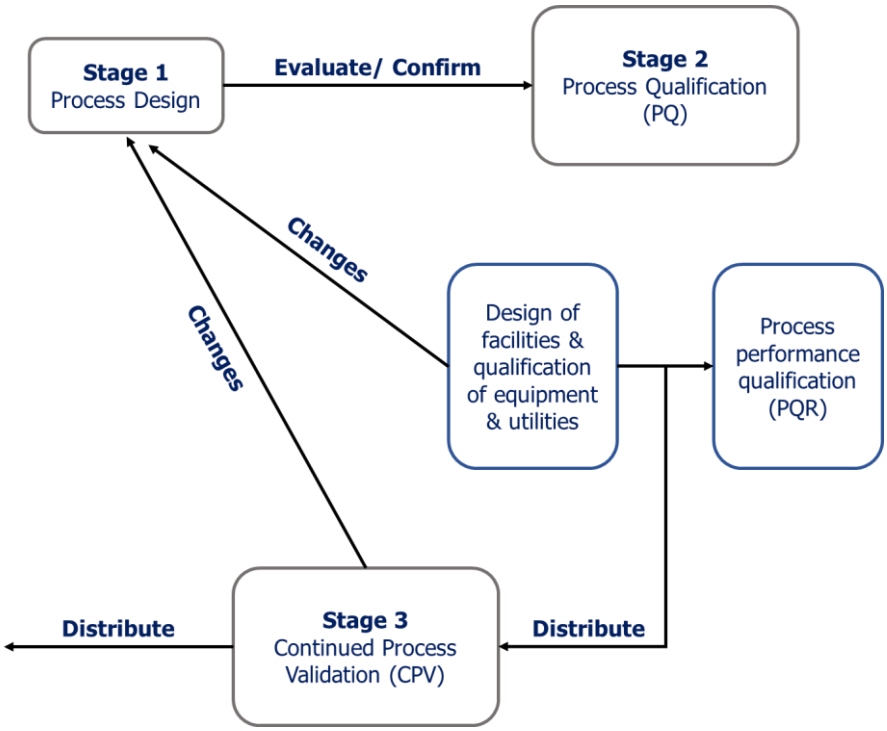

Figure 11: Process Validation Procedure

5.8 Documentation

As it is already evident from the above discussed sections, the importance of proper documentation during each step of validation lifecycle is crucial in order to enable effective communication in large, complex, lengthy and multidisciplinary projects like the ones taking place in the pharmaceutical industry [21].

One of the most important documents (if not the most important) is the Validation Master Plan (VMP). The company's philosophy and point of view, it's structure, intentions and approaches regarding performance assessment, are summarized here. It is drawn up by upper management and should be brief, precise and to the point [11]. All objectives and approved activities are highlighted and all actions to ensure compliance with regulatory requirements are listed. The entire validation layout is outlined in this document [14]. It is very important that information mentioned in other documents is not repeated but instead reference is made to the corresponding protocols, documents, SOPs, policies etc. [11].

The VMP should always be prepared prior to the beginning of the new financial year to avoid error and delays [18].

At the minimum, the below data should be included in the Validation Master Plan:

- Title page with approval signatures and dates
- Table of contents
- Abbreviations and glossary
- Validation policy
- Philosophy, intention and approach to validation
- Roles and responsibilities of relevant personnel
- Resources to ensure validation is done
- Outsourced activities (selection, qualification, management through lifecycle)
- Deviation management in validation
- Change control in validation
- Training
- Scope of validation
- Documentation required in qualification and validation such as procedures, certificates, and protocols
- Premises qualification
- Utilities qualification
- Process validation
- Cleaning validation
- Personnel qualification such as analyst qualification
- Analytical method validation
- Computerized system validation
- Establishing acceptance criteria
- Lifecycle management, including retirement policy
- Requalification and revalidation
- Relationship with other quality management elements
- Validation matrix
- References [14], [11]

Another very important piece of documentation is the validation protocol, which must too be number, signed and dated and providing at least the following information:

- Title
- Objective and scope
- Responsibilities
- Protocol approval
- Validation team
- Product composition
- Process flowchart
- Manufacturing process
- Review of equipment / utilities
- Review of raw materials and packing materials review of analytical and batch manufacturing records
- Review of batch quantities for validation (raw materials)
- Review of batch quantities for validation (packing materials)
- HSE requirements

- Review of process parameters validation procedure
- Sampling location
- Documentation
- Acceptance criteria
- Summary
- Conclusion [11], [14]

Moving forward, after the validation is completed, a validation report must be drafted, including the following subjects:

- Title and objective of the study
- Reference to protocol
- Details of materials
- Equipment
- Programs and cycles used
- Details of procedures and test methods
- Results (compared with acceptance criteria) and
- Recommendation on the limit and criteria to be applied on future basis [12]

Other documents which are related to validation and qualification activities may include but are not limited to:

- Standard Operating Procedures (SOPs)
- Specifications
- Risk assessments
- Process flow charts
- Operator manuals
- Training records
- Calibration procedure and records
- Statistical methods and results etc. [14]

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Conclusions

The history of medicine is almost as old as the history of mankind. Throughout the ages, it has evolved to a highly sophisticated science. At the same time, the pharmaceutical industry has grown to be one of the most vigorous, complex, high revenue generating sectors and a great number of people is linked or impacted directly or indirectly by it.

Unfortunately, a lot of tragical events have taken place during the evolution of the pharmaceutical industry, mostly due to lack of proper quality assurance and of some form of official control. This has led both the public and official authorities to realize the need for a strict regulatory framework. As a result, various laws and regulations have been created both nationally and internationally. Today, most countries have their own set of laws governing pharmaceutical production (some more strict than others) and attempts are made to harmonize these regulations via transnational agreements and mutually acknowledged international bodies. These regulations are commonly known as Good Manufacturing Practices and lay out the requirements for producing products of adequate quality in a recurring way with a high level of confidence. The most well-known of these GMPs are analyzed throughout this thesis, including but not limited to the ones issued by FDA, EMA and ICH (in which both EU and USA are part of) and are more directly linked to western countries, WHO's GMPs (more moderate and thus most commonly adopted by developing countries), as well as the ones provided by the UK (formerly operated under the EU legislation but now paving its own way after the Brexit), China (receiving ever increasing importance) and PIC/S.

Good Manufacturing Practices, are often written in an abstract way, providing minimum demands and requirements which needs to be addressed, while not offering a plan to cover them. This gap is filled by the guidelines for industry which are issued by national authorities and international bodies. One such example, which is further examined on a chapter-to-chapter basis as part of this dissertation, is the guidelines of the EMA.

A very important aspect in achieving constant product quality are the assets (processes, equipment, methods, etc.) incorporated by pharmaceutical companies during the production lifecycle. These assets can be the source of increased or decreased costs, high or low efficiency and ultimately the ability to constantly provide products with high quality. The concept of validation is used to ensure in a documented way that a

process does what it was designed to do, during every process run and under all conditions (inside pre-determined range). There are different types of validation, performed by personnel with specific responsibilities and are discussed in detail above. At the same time, all the benefits and requirements of and for a successful validation are relayed and a list and contents of the most necessary validation's documents is provided.

While reading the relevant literature and composing the dissertation in question, it was evident that great progress has been made in the path of achieving quality assurance in the pharmaceutical industry throughout the years. Nonetheless, there are still parts of the world where regulation remains loose, and loopholes are created and often exploited in an internationalized industry like the pharmaceutical one. Often, profit is put before quality and safety, even when such a sensitive product is in line. At the same time, a strict regulatory framework and the need for high expertise for complying with it, are frequently used for creating entry barriers for the competition rather than being an opportunity for improvement and quality assurance. As a result, greater efforts should be made towards global harmonization and enforcement of Good Manufacturing Practices, and this can be more easily and efficiently achieved through international regulatory and supervisory bodies (existing or new ones). Developing countries should be encouraged to apply tested GMPs and valuable knowledge must be transferred via elusive guidelines.

Finally, the concepts of validation and qualification can be confusing or even overlapping in many cases of the existing literature, making it difficult for someone without sufficient experience to delve further into the subject. More attention could be given to further clarification of these terms and notions.

This thesis has been a systematic attempt to aggregate and relay the main points of the international regulatory frameworks and the corresponding guidelines into one place while further indulging in the European one, since Greece is directly affected by it. At the same time, an effort was made to analyze the complex concepts of validation and qualification and their correlation in terms of their significance, requirements, competences and personnel involved, different types of validation and necessary documentation.

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