**History of GMP and Kaizan Risk management**

 **Thesis**

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**Introduction**

 Good Manufacturing Practice for Medicinal Products (GMP)" is a set of rules for the production of high-quality and safe medical products, in particular medicines such as medical devices, diagnostic products, food products, food additives and active ingredients. The first version of the GMP standards was developed in the USA in 1963, after some time international GMP rules appeared, recommended by WHO for use in all countries of the world in 1969. In the 70s (and later in the 80s), the Soviet Ministry of Health repeatedly raised the issue of the need to fulfill WHO recommendations and the introduction of GMP in the USSR (Greene and Rourke, 2006).

**History of GMP**

 Most of the GMP rules were enacted in response to tragic circumstances to avoid similar situations in the future. It does not represent a comprehensive history of creating and implementing GMP rules but reflects its significant milestones.

**Early 20th century**

In 1905, the book "Jungle" was published, which became a kind of catalyst for changes in the public consciousness. To a large extent, the adoption in 1906 of the Law on the quality of food products and medical preparations was made possible by the fact that during the last 25 years Harvey Wiley (later the chief chemist of the Office of Chemistry at the US Department of Agriculture, who was the predecessor of the FDA, was designed to enforce this law) and his team insisted on its necessity. The law promoted the creation of one of the first state control bodies in the field of food and medicine, now known as the FDA(The Food and Drug Administration) also authorized the confiscation of illegal (falsified) foods and medicines. By the way, the production of biological products was first settled by law for several years before the publication of the book “Jungle”, when at least 12 children died from diphtheria antitoxin, which was infected with active (living) tetanus bacteria. Congress responded to this tragedy by adopting the Biological Actin 1902, according to which it was necessary to inspect the activities of their producers and sellers, as well as to test biologics for purity and efficiency (Chowdary and George, 2011).

**The 1930s**

In 1933, the FDA organized an exhibition at which products, cosmetics, medical preparations and devices harmful to human health were presented. Called the “American Fear Room,” the exhibition was designed to demonstrate the flaws of the 1906 law. Sulfa drugs first appeared in 1935, and many manufacturers began to produce new anti-infective drugs. One company decided to use diethylene glycol, a toxic solvent and a chemical analog of antifreeze in oral sulphanilamide elixir. Until they found out what was happening, 107 people died, many of them children. In response to this tragedy, the United States Congress in 1938 passed the Food, Drug, and Cosmetics Act. For the first time, manufacturers began to demand confirmation of the safety of their products before they became commercially available. This law has significantly expanded the powers of the FDA for the supervision of cosmetics and therapeutic equipment, as well as for conducting detailed inspections of enterprises. The law has tightened food standards and allowed, in case of a violation of the rules and to enforce a halt in production as an additional punitive measure, in addition to the existing confiscation of products and criminal prosecution.

**The 1940s and 50s**

In 1941, a tragedy occurred that had nothing to do with the events of the Second World War. About 300 people died and suffered from taking sulfathiazole tablets, to which the depressant Phenobarbital was added. This incident forced the FDA to fundamentally revise the requirements for the production and quality control of medicinal products and largely contributed to the development of the GMP system. The Law on Health Care, adopted in 1944, solved a large number of problems, including in the sphere of regulating biological products and controlling infectious diseases. After analyzing the samples, the FDA issued a permit to sell this batch. This practice began in 1941 for insulin and in 1945 for penicillin, and then spread to all antibiotics. Mandatory certification of each batch of manufactured drugs was canceled only in 1983 (Kots, Martin, Sharina and Murad (2009).

**The 1960s**

Thalidomide was introduced on the European market, as a sleep aid medication and a drug to combat morning sickness during pregnancy. However, the drug on the American market was not allowed. Responsible for deciding to ban the drug was a female scientist Francis Kelsey. In 1962, US President John F. Kennedy presented her with an award "For Distinguished Service to the Fatherland" - the highest award that civil servants can receive. The case of Thalidomide stirred up public opinion. Two legislators - Kefawar and Harris - insisted on the adoption of strict amendments by the Congress, obliging companies to ensure not only the safety of their products but also to confirm the therapeutic properties of the drugs, in other words - their effectiveness. Now the drugs had to prove their effectiveness before entering the market. Manufacturers were also required to report incidents of negative side effects. In addition, from this point on, the FDA was empowered to regulate advertising for prescription drugs.

**The 1970s**

In 1970 became a turning point in the legislative regulation of products. In 1978, the final version of the GMP rules for medical products and medical devices was approved. The purpose of the introduction of these rules was to ensure the safety and effectiveness of all types of products.

"The rules ... contain a minimum of GMP requirements for premises, production methods and methods of controlling production, processing, and packaging of drugs to meet their safety requirements, as well as their stated performance and purity characteristics."

A few years earlier, amendments to medical devices, issued in 1976 in the form of a law, expanded the powers of the FDA to control medical equipment. These amendments were forced by incidents with intrauterine devices for the prevention of pregnancy, which was used by more than 2 million women. Amendments to medical equipment obliged its manufacturers to submit to the FDA information about their safety and efficacy before being released to the market. Moreover, the law enshrines the system of product supervision before and after its appearance on the market. Supervision included FDA inspections to ensure that companies follow GMP rules, maintain proper records of developments and products, and handle complaints. Today, these provisions seem to us completely natural.

**The 1980s and 1990s**

In 1982, 12-year-old Mary Kellerman complained to her parents about a cold. The parents gave the girl Acetaminophen capsule Tylenol Extra-strength, and after a few hours, she died. After this incident, the FDA introduced special packaging guidelines for all OTC drugs to ensure their protection against poisoners and incorporated these prescriptions into GMP regulations. In 1983, the US Congress passed a law against malicious attackers, turning the opening of finished products into a criminal offense.

Interestingly, in the past, 70-80% or more of the active pharmaceutical ingredients used in the manufacture of medicines in the United States were brought from abroad, where production standards are not so carefully observed. For this reason, the European Union, together with the United States, promptly published a draft guide for manufacturers of active pharmaceutical ingredients. The draft of the document "Guidelines for the production: production, processing or storage of active pharmaceutical ingredients" was released in 1998. The rules of GMP medicines also apply to the manufacture of active pharmaceutical ingredients. In 1990, proposals for amending the rules of GMP medicines were published. In accordance with the final rules of electronic accounting, control mechanisms are necessary to ensure the safety and accuracy of all computer systems used.

**A look into the future**

Various papers submitted to the FDA website, provide guidance on the necessary conditions to make changes to the already approved use of drugs. This study regulates the right to make changes in the regulatory documents about the preparation depending on the type changes. For biologics, companies are now ready to "comparative protocols" to conform to the proposed changes. In this regard, let us remember that each of us, in any way connected with the pharmaceutical industry, has its share of responsibility. We notice in our daily work those things that other people do not see, or we can make the right conclusion faster than people who are not engaged in pharmaceuticals.

**History of Kaizen**

 *“In Japanese, the word "kaizen" means "improvement." Kaizen philosophy suggests that our life as a whole (working, social and private) should be focused on continuous improvement” (*Matusova, 2016)*.*

The kaizen process brings about improvements that are small and incremental, and significant results can be seen only after a certain period of time. Many organizations across the world have adopted kaizen management philosophy and have successfully increased the efficiency of their end-to-end supply chains (Matusova, 2016).

With a focus on quality and regulatory compliance that are getting stringent day by day, pharmaceutical companies have been adopting these new strategies. This review focuses on the basic aspects of Kaizen and Lean implementation and highlights a few examples from the pharmaceutical industry. As far as Kaïzen is concerned, the importance of suggestions made by employees through the suggestion system and QC (circle of quality) is often emphasized. According to Imai (1992), Toyota's ex-president, Toyoda, said: "One of the characteristics of Japanese workers is that they use their brains just as much as their hands. Our workers bring us a million and a half suggestions a year and 95% of them are put into practice. In Toyota's atmosphere, the desire for improvement is almost tangible.

**Comparison of GMP and lean**

“*GMP has evolved gradually, however the recent scientific risk-based framework and the process analytical technology (PAT) initiatives, developed by regulatory authorities to support innovation and efficiency in a c GMP environment, suggest a new way of thinking for the 21st century. Since 2001, regulatory authority policies have promoted initiatives designed to increase the availability of new and affordable medicines. This new thinking should help the pharmaceutical industry move towards innovation in manufacturing and alleviate the fear of lean improvement. These fears will only be removed when manufacturers are confident that a successful lean implementation in a c GMP environment can have both regulatory approvals and be technically dependable”.*

**History**

*“Kaizen originated after War 2 (WWII) in Japan in 1950 when management and the government acknowledge that there was a problem in the current confrontation management system and a pending labor shortage. Japan sought to resolve this problem in cooperation with the workforce. The story of Kaizen miracle started in the year 1930s where the founder of Toyota, Sakichi Toyoda which manufactured automatic looms at the time, liked to tell his co-workers:Open the window; it is a big world out there”.*

 The bases for continuous improvement are born, contrary to popular belief, in the United States Indeed, after the Second World War, the United States stands out with a powerful and powerful industry while Japan, ruined, must totally rebuild itself.

 However, the Americans did not exploit the methods that were put in place during the war by Eduard DEMING. The Japanese bought machines in the United States and began to produce. Unlike the Americans, the Japanese modified their machines so that they could produce a maximum of products in order to meet demand under the DEMING cut, in particular, who went to expose his methods in 1950 in a country that was more receptive to these new concepts. The machines were then able to realize a large number of different references with very short change times while using the principles of DEMING by ensuring the presence of management during the implementation of these projects (Hardin and McCool, 2015).

The DEMING Award was created to reward the best companies of the total quality as well as the month of the quality to sensitize the companies on these benefits with the organization of seminars and debates. Japanese products flooded international markets as early as the 1960s and the public was conquered. In fact, Japanese products were cheaper and of equal quality and higher than those of the Americans and Europeans. Japan then became a great industrial power with the development of Masaki IMAI's KAIZEN.

The Americans began to take an interest in these methods of manufacture. Since the early 1980s, DEMING has conducted 250 seminars in the United States that followed nearly 120,000 people by exposing the famous 14 points of DEMING.

 In Europe, it is notably with people like Noël GOUTARD at Valéo that the concepts of continuous improvement became known.

**Conclusion**

There are two features characterize the pharmaceutical industry: it exists to improve the quality of life of people, reduce their suffering and pain, and find a cure for diseases. In addition, it is strictly regulated. In an ideal world, excessive regulation is useless, but, unfortunately, we do not live in an ideal world. Due to a large number of tragedies, many people perceive regulators and industry regulation itself as a system of checks and balances, believing, like me, that we all have a common goal: to put safe and effective products on the market.

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