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A GLANCE TO THE STORY OF GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICALS

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Abstract
Good Manufacturing Process (GMP) is the magic key that opens the door of quality. GMP is an evergrowing process as the new drugs are discovering day by day, but the concept is not new; its roots are very old. Everyone in our industry should know the story of how the GMP has come to be. Most requirements were put in place as a result of tragic circumstances and to prevent future tragedies. These regulations are mandatory for drug manufacturing companies in order to manufacture quality products.
Keywords: GMP, FDA, WHO

Introduction

Good manufacturing practice (GMP) refers to an international set of regulations planned for implementation in the pharmaceutical or drug industries to assure the effectiveness, quality and safety of drug/pharmaceutical products[1]. A glance back at the achievements and the tragedies of the pharmaceutical industries reveals the importance of combining compliance with current good manufacturing practices (GMPs).

Objectives of GMP:

1. To build in quality drugs rather than testing quality.

2. To ensure that products are consistently produced and controlled according to quality standards.

3. To minimise the risks involved in any pharmaceutical production that cannot be eliminated by testing who has a fundamental role in ensuring the final product[1].

Why GMP?

People prescribing or being prescribed a medicine has minimum chance for identifying if it is faulty or not. People who take a drug and the dispensing pharmacist in turn put their trust in manufacturer who has a fundamental role in ensuring that the medicine is fit for its purpose and is safe for use in patients.The following points denotes the essentiality of GMP[2].

1. Unexpected contamination of products causing damage to health or even leading to death.

2. Incorrect labelling that could lead to patients receiving the wrong medicine.

3. Insufficient or excess active ingredient that contributes to ineffective treatment and adverse drug effects.

Golden rules of GMP:

The aims of GMP are to assure quality and patient safety. This should mean that a product of assured quality, potency, purity and safety is produced. The manufacturer will also have a documentation regarding that, every product has passed through a similar protocol without taking any aspect for granted. Active Pharmaceutical Ingredient and Finished Product Manufacturer objectives to operate their company in accordance with the principles of GMP. It is the responsibility of the manufacturer to design the layout for facilities and equipment right from the start. The golden rules of GMP are follows:

- Design and Layout right from the start.
- Validate Processes.
- Write Good Procedure and follow them.
- Identify who does what.
- Keep Good Records.

- Train and Develop Staff.
- Practice Good Hygiene.
- Maintain Facilities and Equipment[3].
- Maintain Records.
- Design Quality into the Whole Product Lifecycle.
- Perform Regular Audits.

It is necessary to follow GMP guidelines in each step of drug discovery and development for a quality product, as the GMP is the one of the method for quality assurance.

Historical development of GMP:

Beginning from the early civilisations people have been concerned with the safety and quality of their food and also their medicine. King John of England proclaimed the first English food law in **1202**, which prohibited adulteration of bread with ingredients such as ground peas or beans.

The 1900s:

Early in this country's history, traveling medicine shows sold bottles of ointment or "Miracle elixir" which is said to be good for aches and pains as well as for catarrh, rheumatism, and gout and of course it completely cured cancer. Those days are long gone for our luck.

In **1901** children who received antitoxin for diphtheria treatment died of tetanus because the horse serum that had been used to prepare the antitoxin were contaminated with tetanus.The importance of the good quality of raw materials was shown as well as the ability of the animal derived materials to spread diseases both which are known and unknown.

In **1902**, thus the **Biological Control Act**, first introduced in USA for regulation of biological products.

In **1905**, a book called *The Jungle* helped to promote public opinion for change.It was written in the book about the Chicago meat packing industry, about the unsanitary conditions in which animals were slaughtered and processed and the practice of selling rotten or diseased meat to the public. *The Jungle* had a major impact on the American public.

In **1906**, Congress passed the original Food and Drug Act, and for the first time it became illegal to sell contaminated food or meat and demanded truth full labelling.

The 1930's:

A **1933** FDA exhibit of dangerous food, medicines, medical devices and cosmetics illustrated the limitations of the **1906** law. The famous exhibits like

(1) a womb supporter that could puncture the uterus if inserted incorrectly,

(2) a weight loss drug that caused death,

(3) a hair remover that caused baldness,

(4) creams and lotions that lead to mercury poisoning,

(5) a hair dye as a source of lead poisoning,

(6) a eyelash dye which blinded woman etc[4]. Sulpha drugs were introduced in **1935**. The usage of di ethylene glycol, a poisonous solvent and a chemical analog of antifreeze, in an oral "elixir of sulphanilamide" by a company, but it was late when the problem was realised, 107 people died and many of them were children.

In **1937** people felt the need for a stronger federal law due to the tragic public health disaster. The first "wonder drug" ,sulphanilamide which was an effective treatment for the diseases such as gonorrhoea and sore throat, was formulated into an elixir for the use of children. Congress passed the **Federal Food and Cosmetics Act (FD&C)** of **1938**. The companies were required to prove that their products were safe before marketing them for the first time.

The 1940's & 1950's:

A tragedy happened in **1941** was not related to World War II. The Insulin Amendment Act requires FDA to test and certify purity and potency of insulin. The distribution of sulpha thiazole tablets tainted with Phenobarbital lead to the death of nearly 300 people. As a result FDA began to revise manufacturing and quality controls the beginning of this was called GMPs. The Public Health Services Act of **1944** has large area of concerns, which includes the regulation of biological products and the control of communicable diseases. During World War II era, batch certification by FDA became a requirement for certain drugs. Every pharmaceutical industry was required to submit samples from each lot to FDA for testing. The permission was given by the agencies for their release. This practice was first begun in **1941** for insulin and in **1945** for penicillin, which was later expanded to all the antibiotics.

In **1955**, Jonas Salk discovered a way to vaccinate against polio. The manufacture of his polio vaccine was taken up by many manufacturing industries. One of them failed to inactivate the virus on a single try. About 60 individuals inoculated polio and 89 of their family members got polio from them. After this incident, ***FDA started ensure safety of the vaccine,*** because vaccination is a prophylactic and a public health measure to protect society from the spread of ailments[5].

Thalidomide was marketed in Europe as a sleeping pill for morning sickness. When the regulatory agencies gave permission to sell these drugs for that indication without having any knowledge about its serious side effects. It turned out to be teratogenic. It having a serious impact on developing foetus. Children whose mothers took this drug in the first trimester were born with severely deformed arms and legs. Thalidomide use led to about 10,000 cases of deformities in infants. Thalidomide galvanised public opinion. Two legislators, Kefauver and Harris, pushed more stringent legislation through Congress that required companies to test and ensure that the products were safe as well as their efficiency in their intended use. Regulating clinical trials, first the drugs have to be tested in animals before humans as required by the amendments. Investigators were responsible of the correct supervision of the drugs under study. Manufacturers must inform and obtain the consent of the participant before testing it on them for investigational purposes. Manufacturers must show the drug to work and report any unexpected adverse effects before going on the market. The authority for the regulation of advertising of the prescription drug was given to FDA. The phrase "Good Manufacturing Practice" was first appeared officially in the **1962** amendment to the Food, Drug and Cosmetic Act.

The 1970s:

The **1970s** were water shed for product regulation. GMPs for medical devices and drugs were made final in 1978. They were intended to help ensuring the efficiency and safety of all products. The regulations contains the minimum good manufacturing practice for methods to be used in, and facilities or controls to be used for , manufacturing, processing, packing or holding of a drug to ensure that such drug meets the requirements of the act as to ensure safety, and has the identity and strength that meets the quality and purity characteristics that it is represented to possess.

The **1972** incident which has taken place in Devonport, UK , resulted in five deaths when the recipients developed infections because of the contamination of the drug products intended to be sterile. Dextrose IV solutions were not found to be uniformly sterile as a result of an unwritten change to autoclave operation, communicated orally between operators. The Clothier inquiry which examined the factors and causes, identified several violations of basic GMP. This event led to the current requirement of the "Documented Evidence".

Few years back The Medical Device Amendments increased the authority of FDA to oversee the medical devices. The incidents involving the contraceptive intrauterine device used by about 2 million women precipitated this law. The product was taken off from the market as it severely injured many users and have led to serious problems like pelvic infections, infertility, and some deaths.

In **1979** Good Laboratory Practices (GLPs) were made final. They are defined as good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for marketing or research permits for products including human and animal drugs, food and colour additives, animal food additives, medical devises for human use, electronic products and biological products which are regulated by Food and Drug Administration. Compliance with this part is intended to assure the integrity and the quality of the safety data filed.

In **1979** due to a lack in chlorides in two soy based formulas caused severe illness in more than 100 children. Manufacturers has to analyse each batch of formula for nutrient levels and make safety checks, code each container with a lot number, conduct stability tests, keep detailed records of production and analysis, and so on.The Medical Devices Amendments requires to provide FDA with safety and effectiveness data for manufacturers of most medical devices before marketing them. The law provides for a system of pre- and post-market oversight, including FDA inspections, to ensure that companies follow GMPs, keep appropriate records on the design and manufacture of their products, and maintain system for handling complaints. These are the provisions we take for granted today.

The 1980s and 1990s:

In **1982**, several people suddenly died because of cyanide poisoning who were the consumers of over-the-counter Tylenol capsules. An intensive investigation of the production records proved that this was not as the result of raw material mix up during manufacturing. The manufacturer notified the public and voluntarily recalled its entire product in and that is now a case of how to respond to a health disaster. Their development scientists began to redesign the capsule to make tampering more difficult and more detectable. The industry as a whole re-evaluated the means of delivery over-the counter medicines. In **1982** regulations started updating. They now require packets which are tamper resistant as to avoid tampering. Over-the-counter pharmaceuticals could have become an unacceptable safety risk without these steps[6].

In **1989,** an outbreak of toxic reactions to over-the-counter L-Tryptophan, a dietary supplement, resulted in thousands of less severe reactions that led to 38 deaths. A manufacturing process change that increased the level of a harmful byproduct resulted in this incident. The toxicity has been caused by a dose that was previously

been safe. On response to this event was the new requirements for evaluation of minor impurities and the clarification of requirements for characterising drug impurities. In the biological products area, extensive guidances have been issued on how to establish comparability when process, facility, or other changes are made. Interestingly enough, some 70-80% or more of the APIs used to manufacture products for United States coming from sources outside the country, where manufacturing standards may not be rigid.

In the **1990s,** proposed revisions to the GMPs for drugs and biologicals were released. When this article went to press, they do represent FDA's current thinking, as these revisions were not final.

Congress passed the *Generic Drug Enforcement Act* in **1992** to impose penalties on illegal acts involving abbreviated drug applications. The **1992** Act resulted from a bribery case in which executives of one or more generic companies bribed FDA reviewers.

The **1996** ICH E6 guidance on good clinical practices has become the standard on performing the human clinical trials.In 1996 proposed revision for US CGMPs for Drugs and Biologicals for validation blend uniformity, prevention of cross contamination, and handling out-of-specification came.

1997 Electronic Records Final Rule requires controls that ensure security and integrity of electronic data.

1998 Draft Guidances: Both European Union and United States recently published draft guidance for the manufacture of drugs. The draft document was released in 1998 for the "Guidance for Industry related to Manufacturing, Processing, or Holding of Active Pharmaceutical Ingredients"[6].

Thus a glance of major points involved in the chronological development of GMP is notified.

Conclusion:

The health of citizens of any country depends on the availability of safe, effective and affordable medicines[7]. Today, more people than ever are taking drugs. Adverse drug events are more common and some lots of product which initially have met specifications are released to the public, and are later recalled due to quality reasons.

It is necessary follow GMP guidelines in every single step of drug discovery and development. The incidence of safety problems is quite low now a day, as a result of GMP systems.

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