ISSN 0974-3618 (Print) **www.rjptonline.org**
0974-360X (Online)

REVIEW ARTICLE

Evolution of GMP in Pharmaceutical Industry

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ABSTRACT:
This Article gives holistic view of Birth of Good Manufacturing Practices (GMP) in Pharmaceutical Industry. Most of GMP requirements were put in place as responses to tragic incidents to prevent future tragedies. This article exhibit how year after year the laws and regulation were enforced to manufacture the medicines. Though the birth of GMP took place long ago but now the time requires to harmonize the regulatory requirement across the globe. This article is not an all-inclusive history but a representative one.

KEYWORDS: GMP, Drugs, Medicines, Contamination, Side effects, Commodity, Compliance

INTRODUCTION:

Medicines are perhaps as old as Mankind and the understanding how their quality has to be ensured has evolved gradually over the time. Unfortunate events have prompted the development of medicines regulations more than the evolution of a knowledge base. Drugs are not ordinary consumer products and in most of the instances, consumers are not in a position to make decisions about quality of the drugs, hence the production of medicines, their distribution and dispensing also requires special knowledge and expertise [1].

Since our ancestors began trading several years ago, counterfeit and substandard medicines have been a recurring problem, with history punctuated by crises in the supply of anti-microbial, such as fake cinchona bark in the 1600s and fake quinine in the 1800s. Unfortunately this problem persists, in particular bothering innocent patients in 'developing' countries. Poor-quality drugs contribute to a 'crevasse' between the enormous effort in therapeutic research and policy decisions and implementation of good-quality medicines.

Received on 09.01.2017 Modified on 27.01.2017
Accepted on 05.02.2017
Research J. Pharm. and Tech. 2017; 10(2): 501-506.

Globalization of the pharmaceutical industry has the potential to rapidly spread poor-quality medicines worldwide before adequate detection and intervention are possible. There are two main categories of poor-quality medicines: substandard and counterfeit. Substandard products arise as a result of lack of expertise, poor manufacturing practices, or insufficient infrastructure, whereas counterfeits are the 'products' of criminals. Counterfeits may contain no active ingredient, incorrect ingredients, or toxins. The amount of active ingredient does not provide sufficient information to accurately determine if a medicine is counterfeit; inspection of the packaging is also required as mislabelling is a key part of the definition and counterfeits with fake packaging but the correct amount of active ingredient have been described. In many reports, it is unclear if poor-quality medicines are counterfeit or substandard, but it is important that they are correctly classified because they have different origins and different solutions. Inadequate enforcement, lenient penalties, corruption, 'spaghetti-like' trade arrangements, unregistered medicines, and ignorance of poor-quality medicines among the public and health workers worsen the situation.

To ensure that quality is consistently achieved in the drug product, Good manufacturing practices have to be followed. To obtain and maintain GMP compliance,

every manager and supervisor should provide frequent, meaningful GMP reminders, train and develop all employees, and fully participate in formal, on-going training programs. Senior management must make it clear through their actions that following GMPs is the only way their company does business. If you want people to move toward regularly following GMPs, they have to know why the regulations came about and what's in it for all of us as consumers to see them followed. Most requirements were put in place as responses to tragic circumstances and to prevent future tragedies [2].

Drugs / Medicines

The Food, Drug & Cosmetic (FD&C) Act defines drugs as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." It is the intended use that determines whether something is a drug. Thus, foods and cosmetics may be subject to the drug requirements of the law if therapeutic claims are made for them. The FD&C Act prohibits adulteration or misbranding of any drug and requires that "new drugs" be reviewed and approved by FDA before they go to market. Drug applications typically fall into three categories in USA: a new drug application, a new animal drug application, or an abbreviated new drug application for generic products.

History of Medicine Regulations

Regulations over product quality, patient safety, and efficacy were born reactively from tragedies over the past 110 years and now becoming more proactive.

The 1900s

In 1905, a book called "The Jungle" helped catalyse public opinion for change. The book was written by Upton Sinclair, a "muckraker" journalist and social reformer. He wrote 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. He also reported that ground meat sometimes contained remains of poisoned rats and even unfortunate workers who fell into the machinery. Sinclair's main interest was in bringing attention to the miserable working conditions and the plight of the impoverished factory workers may of whom were immigrants [2].

The *Jungle* had a major impact on the American public. Congress passed the Pure food and Drug Act in 1906, and for the first time it became illegal to sell contaminated (adulterated) food or meat. Also for the first time, labelling had to be truthful (no one could "promise the moon and the stars" on a label anymore) [2].

Biologic products were first regulated a few years before the jungle, when at least 12 children died from a diphtheria antitoxin that was contaminated with live tetanus bacilli. US Congress responded to that tragedy by passing the biologics control Act of 1902, which required inspections of manufacturers and sellers of biological product and testing of such products and testing of such products for purity and strength [2].

The 1937 - Elixir Sulfanilamide Disaster

In 1937, one company in Tennessee, USA began selling bottles of Elixir Sulfanilamide, a liquid version of a popular antibiotic of the day. But more than 100 people died after taking the drug, and investigators from the US Food and Drug Administration (FDA) identified the drug's solvent, diethylene glycol, as the killer [3].

In response, US Congress passed the Federal Food, Drug and Cosmetic (FD&C) Act of 1938. For the first time, companies were required to prove that their products were safe before marketing them. It extended FDA oversight to cosmetics and therapeutic devices, explicitly authorized factory inspections, required standards for foods, and added injunctions to previous penalties of seizures and criminal prosecutions [2].

The 1941 – Sulfathiazole Disaster

In 1941, Nearly 300 people were killed or injured by Winthrop's sulfathiazole tablets, a sulfa drug tainted with the sedative, phenobarbital. Each sulfathiazole tablet was contaminated with about 350 mg of phenobarbital. Investigation by US Food and Drug Administration and the findings resulted into actions. The incident was influential in the introduction of Good Manufacturing Practices for drugs [4]. Winthrop became the first company since the 1938 law was passed to have its new drug application suspended[15].

That incident caused FDA to revise manufacturing and quality control requirements drastically, leading to what would later be called GMPs. The Public Health Services Act, passed in 1944, covered a broad spectrum of concerns, including regulation of biological products and control of communicable diseases[2].

Batch certification by FDA became a requirement for certain drugs. It required companies to submit samples from each lot to FDA for testing and the agency would give permission for their release. That practice, begun in 1941 for insulin and 1945 for penicillin, was later expanded to include all antibiotics. By 1983, the requirement for batch certification of drug was dropped[2].

The 1962 - The thalidomide disaster

The thalidomide disaster is one of the darkest episodes in pharmaceutical research history. The drug was marketed as a mild sleeping pill safe even for pregnant women. When regulatory agencies gave permission to sell the drug for that indication; they had no knowledge of its serious side effects. It turned out to be teratogenic and it caused serious deformities in developing foetuses. Children whose mothers took thalidomide in the first trimester were born with severely deformed arms and legs. An estimated 10,000 case of infant deformities with malformed limbs in Europe were linked to thalidomide use[3].

Picture 1: Babies with deformities due to Thalidomide tragedy

The product was not allowed on the market in the United States by Frances Kelsey. In 1962 President Kennedy awarded her the President's Distinguished Federal Civilian Service Award, the highest honour [3].

Two legislators, Kefauver and Harris, pushed more-stringent legislation through congress that required companies to test not only to ensure that products were safe, but that they were efficacious for their intended uses. Regulating clinical trials, amendments required drugs to be tested in animals before people. They made investigators responsible for supervising drugs under study. Manufacturers were expected to inform participants if a drug was being used for investigational purposes and to obtain their consent before testing it on them. Drugs had to be shown to work before going in the market. Manufacturers were required to report unexpected harm (adverse events) and USFDA was given authority to regulate advertising of prescription drugs [2].

The 1970s

GMPs for drugs (21 CFR Parts 210 and 211) and medical devices (21 CFR 820) were made final in 1978. They intended to help ensure the safety and efficacy of all products for US consumers:

The regulations contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess [6].

Good Laboratory Practices (GLPs) were made final in 1979. They are defined follow:

Good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and colour additives, animal food additives human and animal drugs, medical devices for human use, biological products, and electronics products. Compliance with this part is intended to assure the quality and integrity of the safety data filed[7].

The 1982 - Tylenol capsules Disaster

In 1982, twelve-year-old child died after taking Extra-Strength of Tylenol capsules (acetaminophen capsules). Later on, six another people died and Investigators soon discovered the Tylenol link. Urgent warnings were broadcasted, and police drove through Chicago neighbourhoods issuing warnings over loudspeakers.

Johnson & Johnson distributed warnings to hospitals and distributors and halted Tylenol production and advertising. On October 5, 1982, it issued a nationwide recall of Tylenol products; an estimated 31 million bottles were in circulation. The company also advertised in the national media for individuals not to consume any products that contained acetaminophen.

The acetaminophen tragedy had a major impact on the industry and the 1982 incident inspired the pharmaceutical, food, and consumer product industries to develop tamper-resistant packaging, such as induction seals and improved quality control methods [8].

FDA issued tamper-resistant packaging regulations for all OTC human drug products and incorporated them into the GMPs; US Congress passed the Federal anti-Tampering Act in 1983, making it a crime to tamper with packaged consumer products [9].

The 1986 - J J Hospital, Mumbai, India Glycerin Adulteration Scam[16]

Between January 21 and February 7, 1986, 14 patients died in J.J. Hospitals in Mumbai from a cause totally unrelated to the diseases that brought them there. They died of poisoning by the adulterated glycerol given to

them. The toxic adulterant was diethyl glycol which was present in a concentration of 18.5% - over three times the lethal dose. Rapid necrosis of the kidneys took place and the unfortunate victims succumbed to acute renal failure. This adulterated glycerol, meant for industrial consumption, was sold by Kailash Company to Alpana Pharma, with the former knowing that it was to be used for medicinal purpose. The licensing authority, the drug testing laboratory, the tender committee, the pharmacology department and the highest authorities in J.J. Hospitals were indicted.

The 1989 - Generic Drug Scandal [10]

In 1989, a major scandal erupted involving the procedures used by the USFDA to approve generic drugs for sale to the public. Charges of corruption in generic drug approval first emerged in 1988, in the course of an extensive congressional investigation into the FDA. Investigation discovered that several manufacturers had falsified data submitted in seeking FDA authorization to market certain generic drugs. In April 1989, the USFDA investigated 13 manufacturers for irregularities; and dozens of drugs were eventually suspended or recalled by manufacturers.

At the outset of the generic drug scandal uncovered in the late 1980's FDA developed an administrative Application Integrity Policy. At or about the same time, legislation (the Generic Drug Enforcement Act [GDEA] of 1992), provided for debarment of individuals convicted of certain felony offenses. This meant that an individual that was convicted could be debarred permanently from providing directly or indirectly any services in any capacity to a firm in the pharmaceutical industry.

The 1996 – Mix up of Glibenclamide in India [16]

The FDA in Maharashtra, India ordered a nation-wide recall of the antibacterial drug COMSAT FORTE, a brand of co-trimoxazole, of Boehringer-Mannheim (India) Limited when it was found to contain the antidiabetic ingredient Glibenclamide as a result of mix-up in raw materials on the shop floor of the manufacturing plant. Rather than cure infections, the tablets caused a drastic fall in blood sugar and blood pressure, and 62 people turned critical after using it at an eye camp in Ahmednagar on August 16, 1996. Although the deadline for recall expired on September 5, the drug claimed 2 lives in Kolar, Karnataka, five days later. Police issued arrest warrant against 12 employees of the company.

The 2008 - Heparin Contamination [13,14]

Serious injuries and deaths (81) have been associated with the use of heparin, a blood-thinning drug that contained Active Pharmaceutical Ingredient (API) from China. The adverse events have included allergic or hypersensitivity-type reactions, with symptoms such as low blood pressure, angioedema, shortness of breath, nausea, vomiting, diarrhoea, and abdominal pain.

In February 2008, Baxter Healthcare Corporation recalled multi-dose and single-dose vials of heparin sodium for injection, as well as HEP-LOCK heparin flush products. In April 2008, after extensive analysis and screening, FDA identified the contaminant over-sulfated chondroitin sulfate (OSCS) in heparin API manufactured in China. OSCS contamination of heparin appears to be an example of intentional adulteration and has also been referred to as economically motivated adulteration—i.e., heparin appeared to be intentionally contaminated with OSCS to reduce the cost of production. In response, USFDA issued Guidance "Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality". This guidance provides recommendations that will help API manufacturers, pharmaceutical and medical device manufacturers of finished products, re-packers, and others, to better prevent the use of crude heparin that might contain over-sulfated chondroitin sulfate (OSCS) or non-porcine ruminant material contaminants [17].

Evolution of GMP – a Summary[2,12]

1500	Ebers Papyrus, Egyptian manuscript pertaining to pharmacy and therapy.
1546	The Nuremberg Pharmacopoeia (Dispensatory of Valerius Cordus) is perhaps the first to become "official".
1618	First London pharmacopoeia is published.
1736	First law related to pharmacy in America is enacted in Virginia.
1821	Philadelphia College of Pharmacy is founded as the first local association and school of pharmacy in the United States.
1848	First American code of pharmaceutical ethics prepared by Philadelphia College of Pharmacy. First drug import law enacted by congress to curt adulterations.
1852	American Pharmaceutical Association is founded as the first national organization.
1865	First international pharmaceutical conference is held in Brunswick, Germany.
1888	First National Formulary issued by American Pharmaceutical Association.
1902	First International Pharmacopeial Conference held at Brussels, Belgium.
1906	Federal Food and Drugs Act passed in the US.
1912	First Assembly of International Pharmaceutical Federation (The Hague, Netherlands).

1938	Federal Food, Drug and Cosmetic (FD&C) Act Tragedy: Sulphanilamide made with poisonous solvent causes 107 deaths. Result: manufactures to prove the safety of products before marketing.
1941	Two unrelated events Insulin Amendment requires FDA to test and certify purity and potency of insulin. Tragedy: nearly 300 deaths and injuries from distribution of sulfathiazole tablets tainted with phenobarbital. Result: FDA revises manufacturing and quality controls drastically, the beginning of what will later be called GMPs.
1962	Kefauver-Harris Drug Amendments (Important amendments of the US Food, Drug, and Cosmetic Act). Tragedy: Thalidomide causes birth defects in thousands of European babies. Result: Manufactures must prove efficacy of products before marketing them and ensure stricter control over drug testing.
1975	Official drug standardization program is unified by Us Pharmacopeia absorbing National Formulary.
1978	CGMPs Final rules for drugs and devices (21 CFR 210-211 and 820) Establishes minimum current good manufacturing practices for manufacturing, processing, packaging, or holding drug products and medical devices.
1979	GLPs Final Rule (21 CFR 58) Establishes good laboratory practices for conducting nonclinical laboratory studies that support application for research or marketing permits for human and animal drugs, medical devices for human use, and biological products.
1982	Tamper-resistant Packing Regulations issued by FDA to prevent poisonings such as deaths from cyanide placed in Tylenol capsules. The Federal Anti-Tampering Act passed in 1983 makes it a crime to tamper with packaged consumer products
2005	Formation of the **Drug Safety Board** is announced, consisting of FDA staff and representatives from the National Institutes of Health and the Veterans Administration.

Post 1980s, USFDA began publishing a series of guidance documents that have a major effect on out interpretation of current GMPs. These guidance's are issued to define the FDA expectation from the pharmaceutical industries in order to manufacture safe and quality drug substances and drug products.

Future of Pharmaceutical industry - International Conference on Harmonisation [11]

The birth of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference.

The Topics selected for harmonisation were divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorising new medicinal products.

The ICH is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide. ICH's mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

The realisation that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. However in many cases the realisation was driven by tragedies, such as that with thalidomide in Europe in the 1960s.

For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. The industry, at the time, was becoming more international and seeking new global markets; however the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally. The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of health care, escalation of the cost of R&D and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.

CONCLUSION:

Drug Product is extra ordinary commodity for the human beings to fight against the diseases hence safety and quality is foremost requirement while manufacturing these medicines. Safety of the medicine shall be established right from the development stages before given to human beings. Once proved safe for human consumption, quality of the medicines has to be ensured while manufacturing of the medicine following good manufacturing practices. We have seen through the history that how GMP has evolved reactively after tragedy occurred one after another. Now the world is global village, hence it is very important to have uniform guidance and practices being followed across the world

to produce the consistent quality without further damage to the human life.

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