REVIEW

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Pharmaceutical GMP: past, present, and future – a review

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Good Manufacturing Practice (GMP) is a set of regulations, codes, and guidelines for the manufacture of drug substances and drug products, medical devices, in vivo and in vitro diagnostic products, and foods. GMP term that is recognized worldwide for the control and management of manufacturing and quality control testing of pharmaceutical products. Everyone in the pharmaceutical industry should know the story of how the good manufacturing practices (GMPs) have come to be. Most requirements were put in place as responses to tragic circumstances and to prevent future tragedies. To obtain and maintain GMP compliance, one should know the precedent of the GMP. The present review highlights past, present and future of GMP.

1. Introduction

People prescribing or being prescribed a medicine have little chance of detecting if it is faulty or not. People who take a medicine trust the doctor who wrote the prescription and the pharmacist who dispensed it. The doctor and pharmacist in turn put their trust in the manufacturer who has a fundamental role in ensuring that the medicine is fit for its purpose and is safe to use (Learoyd 2005).

GMP tries to ensure that the quality is built into the organization and the process involved in manufacturing. The activities involved in achieving quality cover much more than the manufacturing operations themselves. There must be clear written specifications for the materials, the packaging and the products themselves. There must be clear written instructions and procedures covering processing and testing, handling, storage, receipt and dispatch. Suitable premises, equipment and trained staff must be specified and made available (Learoyd 2005).

Today, more people than ever are taking pharmaceuticals. Adverse events are common and some lots of product which initially have met specifications are released to the public, and are later recalled due to quality concerns. However, the incidence of safety problems is quite low as a result of GMP systems, talented people and the use of advanced technologies (Shadle 2004).

2. Tragic incidents of 20th century vs. birth of GMP

In 1901 children who received antitoxin for diphtheria treatment died of tetanus because the horse serum that had been used to prepare the antitoxin was contaminated with tetanus. Thus, the importance of high-quality raw materials was demonstrated, along with the ability of animal-derived materials to pass diseases both known and unknown. *The Biologics Control Act was passed in 1902,* to improve the assurance of safety and purity of sera, vaccines, and other biological products. The Food and Drugs Act was first passed and put into law in 1906 and revised as the Food, Drug and Cosmetic Act of 1938 (Shadle 2004).

In 1905, a book called *The Jungle* helped catalyze public opinion for change. "Muckraker" and social reformer Upton Sinclair wrote about the Chicago meat packing industry – 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, many of whom were immigrants. *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 (Shadle 2004).

Syrup to calm "colicky" babies and "tonics" for adults often contained alcohol, opium, or morphine, which addicted many people who used them. So the 1906 Act also required selected dangerous ingredients to be labeled on all drugs. Inaccurate or false labeling was called misbranding, and that became illegal (Immel 2005).

A 1933 FDA exhibit of dangerous food, medicines, medical devices, and cosmetics illustrated the shortcomings of the 1906 law. "America's Chamber of Horrors" included a womb supporter (also used as a contraceptive) that could puncture the uterus if inserted incorrectly; a weight-loss drug that caused death; a hair remover that caused baldness, even if not used on the head; lotions and creams that could cause mercury poisoning; hair dyes that could cause

lead poisoning; and an eyelash dye that blinded women (FDA 2000).

In 1937, a public health disaster tragically drove home the need for a stronger federal law. Sulfanilamide, the first "wonder drug" and a popular and effective treatment for diseases like strap throat and gonorrhea, was formulated into an elixir and marketed for use in children. But the liquid formulation contained a poison, the same chemical used in antifreeze, and it killed 107 people, most of them children. In response, Congress passed the *Federal Food, Drugs and Cosmetic (FD & C) Act of 1938*. for the first time, companies were required to prove that their products were safe before marketing them (FDA overview).

In 1941, nearly 300 people were killed or injured by one company's sulfathiazole tablets, a sulfa drug tainted with the sedative phenobarbital. That incident caused FDA to drastically revise manufacturing and quality control requirements, leading to what would later be called GMPs (Time Line).

Also during the World War II era, batch certification by FDA became a requirement for certain drugs. It required companies to submit samples from each lot to FDA for testing; the agency would then give permission for their release. That practice begun in 1941 for insulin and 1945 for penicillin, was later expanded to include all antibiotics (FDA 1995).

In 1955, Jonas Salk discovered a way to vaccinate against polio. Many manufacturers began making his polio vaccine. One company failed to inactivate the virus completely in a single lot. About 60 inoculated individuals developed polio. After this incident, FDA started ensure safety of the vaccine (Stehlin 1995).

Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. When regulatory agencies gave permission to sell the drug for those indications, they knew nothing of its serious side effects. It turned out to be teratogenic: It caused serious deformities in developing fetuses. Children whose mothers took thalidomide in the first trimester were born with severely deformed arms and legs. An estimated 10,000 cases of infant deformities in Europe were linked to thalidomide use. Thalidomide galvanized public opinion and legislators pushed more stringent legislation through Congress that required companies to test not only to ensure that the products were safe, but that they were efficacious for their intended uses. Regulating clinical trials, the amendments required drugs to be tested in animals before people. They made investigators responsible for supervising drugs under study. Manufac-

Table 1: Chronological development of GMP (Immel 2005; FDA overview; Proceeding 2002)

1902	Biologics Control Act
1906	Pure Food and Drug Act
1938	Federal Food, Drug and Cosmetic (FD & C) Act
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.
1944	Public Health Services Act
1946	Publication by the Pharmaceutical Manufacturers Association of America lf a "Guideline for Good Manufacturing Practices for Pharmaceuticals"
1962	The "Thalidomide Tragedy" leads the US Congress to add GMP to the Food, Drugs and Cosmetic Act. The FDA publishes their first Regulation on Good Manufacturing Practices" – A drug which is not made following GMP is adultered (Contaminated)
1969	The World Health Organization publishes the first universal guideline "Basic Rules for the Manufacture of Pharmaceuticals and the Assurance of their Quality"
1972	The Daily Telegraph published as its main news the recall of 5% Dextrose Infusion Solution after 5 patients die at Devonport Hospital ("The Devonport Hospital Affair")
1974	Allergic reaction due to extremely small traces of penicillin in other drug products lead to demands for separation of penicillin and non-penicillin production.
1974	FDA Starts investigating some US toxicology laboratories and finds evidence of widespread mis-management and even fraud.
1976	FDA publishes their proposals for "Good Laboratory Practices for Non-Clinical Studies"
1975	The EU Directive 75/319 lays down the basic procedures (approximatations) for the registration, trade and compensation for damages for "Medicinal Products" with the EU.
1978	CGMPs Final Rules for Drugs (21 CFR Parts 210–211)
1979	Infant Formula Act
1982	Temper-Resistant Packaging Regulations Issued for OTC Products
1983	The Guide to the Inspection of Computerized Systems in Drug Processing initiates tighter controls on computers and computer validation.
1986	Microbial contamination of an API for veterinary use later causes the deaths of several hundred cattle in Germany.
1987	Guideline on General Principles of Process Validation
1989	FDA discovers mis-management and even fraud in the applications by US generic drug manufacturers in trying to get approval for the sale of their products. (One company even tested not its own product, but the competitor's product against the competitor's products in order to get approval for sale from the FDA.) This leads to PRE-APPROVAL INSPECTIONS (PAIs)
1989	The inspectors of the EU agree on a Guideline for GMP and the EU publishes its Directive on the "Approximation of provisions for GMP in the European Community", i.e. a legal basis is established for pharmaceutical GMP within the European Community.
1991	FDA publishes their "Guide to the Inspection of Bulk Pharmaceuticals" which strongly influences the way in which Starting Materials for pharmaceuticals are produced.
1994	The EU and the FDA open negotiations on the mutual recognition of GMP inspections. (Agreement was finally reached and a DRAFT was signed.
1996	PIC accepts the European industry's GMP Guide
1998	"GMPs for Starting Materials" is added to the ICH work programme to be decided by an Expert Working Group.
2001	ICH Q7A API Guidance ICH's "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (APIs)"

turers were expected to inform participants if a drug was being used for investigational purposes and to obtain their consent before testing it on them (Immel 2005).

The 1972 Devonport, UK, incident resulted in at least five deaths when drug products designed to be sterile became contaminated and recipients developed infections. An unwritten change to autoclave operation, communicated orally between operators, resulted in dextrose IV solutions that were not uniformly sterile. The Clothier inquiry, which examined the causes and contributing factors, identified several violations of what we now consider basic GMP (Shadle 2004). The current requirement of "Documented Evidence" may be driven by this event.

In 1979 more than 100 infants were made seriously ill by a lack of chlorides in two soy-based formulas. Manufacturers has to analyze each batch of formula for nutrient levels and make safety checks, conduct stability tests, code each container with a lot number, keep detailed records of production and analysis, and so on. The food GMPs (21 CFR Part 110), which include special provisions for infant formulas, were finalized in the 1980s (Immel 2005). In 1980, congress passed the Infant Formula Act giving FDA authority to create and enforce standards and specify nutritional requirements for commercial infant formulas.

In 1982, several consumers of over-the-counter Tylenol capsules suddenly died of cyanide poisoning. An intensive investigation of the production records showed that this was not the result of a raw materials mix-up during manufacturing. Rather, tampering apparently occurred on store shelves. A new vulnerability was identified in the supply chain. The manufacturer, Johnson and Johnson, notified the public and voluntarily recalled its entire product in what is now a textbook case of how to respond to a health disaster. Their development scientists went into overdrive to re-design the capsule to make tampering more difficult and more detectable. The industry as a whole re-evaluated the means of delivering over-the-counter medicines. Regulations were started updating in 1982, and they now require tamper-resistant packaging that aids in the detection of tampering. Without these steps, over-the-counter pharmaceuticals could have become an unacceptable safety risk (Shadle 2004).

In 1989, an outbreak of toxic reactions to over-the-counter L-tryptophan, a dietary supplement, resulted in 38 deaths and probably thousands of less severe reactions. The event was the result of a manufacturing process change that increased the level of a harmful byproduct. Doses that had previously been safe now caused toxicity. One response to this event was the clarification of requirements for characterizing drug impurities and new requirements for evaluation of minor impurities. In the biological products area, extensive policy and guidances have been issued on how to establish comparability when process, facility, or other changes are made (Shadle 2004). Chronological Development of GMP regulations has been summarized in Table 1.

3. Current scenario of international GMP

GMP grew out of the realization that end-point quality testing was insufficient to assure the quality of the individual medication unit (the tablet, the capsule, the vial) dispensed to the patient, but rather quality needed to be assured at each step of the manufacturing process to be as certain as possible that each dosage unit met its quality specifications. Prior to this realization, pharmaceutical product quality was assured by pharmacopoeal "end point" testing (GMP worldwide).

Good Manufacturing Practices (GMPs) is that part of quality assurance which ensures that products are consis-

Table 2: Major GMP regulation agencies

Country (Regulatory Agencies)	Product Types Inspected	Web Site / URL
United States (Code of Federal Regulations)	Bulk Pharmaceutical Chemicals, Finished Pharmaceuticals	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm
Europe	Finished Pharmaceuticals, Active Pharmaceutical Ingredients	http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm
Canada (Health Canada)	Finished Pharmaceuticals, Active Pharmaceutical Ingredients	http://www.hc-sc.gc.ca/ahc- asc/legislation/reg/index_e.html
Brazil (National Agency for Sanitary Surveillance, ANVISA)	Finished Pharmaceuticals	http://www.anvisa.gov.br/eng/index.htm
Australia (Therapeutic Goods Administrations, TGA)	Finished Pharmaceuticals, Active Pharmaceutical Ingredients	http://www.tga.gov.au/manuf/index.htm
United Kingdom (Medicine and Healthcare Products Regulatory Agency, MHRA)	Finished Pharmaceuticals	http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeID=369
Germany (Ministry of Health, Labour and Welfare)	Finished Pharmaceuticals, Active Pharmaceutical Ingredients	http://www.mhlw.go.jp/english/index.html
South Africa (Medicines Control Council)	Finished Pharmaceuticals	http://www.mccza.com

Table 3: Links of GMP guidance documents

Country/Agency	Web Site / URL
United States	http://www.fda.gov/opacom/morechoices/industry/guidedc.htm
Europe	http://www.europa.eu'enterprise/pharmaceuticals/eudralex/index.htm
Canada	http://www.hc-sc.gc.ca/ahc-asc/legislation/guide-ld/index_e.html
International Conference of Harmonization	http://www.ich.org
The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)	http://www.picscheme.org/index.php?p=backgr

tently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization or product specification. GMP is concerned with both production and quality control.

Worldwide, there are different official regulatory statements and guidelines, national and international, on Good Manufacturing Practices for pharmaceutical (or "drug" or "medicinal") products. They may be regulations (as in the US, Japan or Korea), directives (as in the EU), guides (as in the UK), codes (as in Australia), or WHO code (as in many Southeast Asia Countries). Out of them, following stands out as being the most influential and most frequently referenced (Patel and Chotai 2006):

- The US Current Good Manufacturing Practices for Finished Pharmaceuticals regulations (the "US cGMPs")
- The Guide to Good Manufacturing Practice for Medicinal Products of the European Union (the "EC GMP Guide") (Eudralex)
- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH 2000).
- WHO good manufacturing practices (GMP 2003).

The other regulation referred by the Indian pharmaceutical manufacturers is Schedule M "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" The Drugs And Cosmetics Act And Rules, India (Schedule 2005).

The glance of major GMP regulatory agencies or guidelines is highlighted in Tables 2 and 3 respectively. The related site contains detailed information pertaining to GMP.

4. Future

The last few years has seen the FDA steer industry further in the direction of a quality-by-design (QbD) approach, and away from the quality-by-testing (QbT) approach traditionally taken by the pharmaceuticals sector. This move has largely been lauded by business as a sensible move likely to ensure consistent quality of the end product. The shift in focus is expected to bring about a well-needed modernization to the sector and allow new ideas the breeding ground needed to flourish. As pharmaceutical manufacturing evolves from an art to a science and engineering based activity, application of this enhanced science and engineering knowledge in regulatory decision–making, establishment of specifications, and evaluation of manufacturing processes should improve the efficiency and effectiveness of both manufacturing and regulatory decision–making, A Process and Analytical Technology (PAT) initiative has been initiated by the FDA and designed to revolutionize and improve many pharmaceutical processes. A regulatory framework, PAT discusses possible routes and opportunities to promote and encourage opportunities for innovation. The FDA has outlined the guidelines of the initiative in a document entitled "Guidance for Industry PAT – A Framework for Innovative Pharmaceutical, Development, Manufacturing and Quality Assurance" (Afnan).

Pharmaceuticals will have an increasingly prominent role in the health care of the future. The health of citizens of the any country depends on the availability of safe, effective and affordable medicines. In the future, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries and ways of doing business such as individualized therapies or genetically tailored treatments. Regulation of the future will also need to meet these challenges, by incorporating new scientific information into regulatory standards and policies. Both industry and regulatory practices will need to be informed by the best techniques of risk assessment and management. "Pharmaceutical cGMPs for the 21st Century" is intended to jump-start progress into this future.

Pharmaceutical manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the efficiency of both manufacturing and regulatory processes. This initiative is designed to do just that through an integrated systems approach to product quality regulation founded on sound science and engineering principles for assessing and mitigating risks of poor product and process quality in the context of the intended use of pharmaceutical products. In this regard, the desired future state of pharmaceutical manufacturing may be characterized as:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Continuous "real time" assurance of quality
- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product (Summary Progress Report).

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