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REVIEW

Quality in the pharmaceutical industry – A literature review

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Abstract *Objectives:* The aim of this study is to:

a. Highlight the most important guidelines and practices of quality in the pharmaceutical industry.
b. Organize such guidelines and practices to create a guide to pave the way for other researchers who would like to dig deeper into these guidelines and practices.

Design: A review was conducted of 102 publications; 56 publications were concerned with the pharmaceutical quality directly while 46 publications were concerned with the general quality practices. The content of those sources was analyzed and the following themes were identified:

a. Research theme 1: Guidelines of the pharmaceutical quality.
b. Research theme 2: General practices recently applied in the pharmaceutical industry.

Main outcome measures: The following guidelines were identified and reviewed: WHO guidelines, FDA guidelines, EU guidelines and ICH guidelines in the research theme I.

In research theme II; the following topics were identified and reviewed: quality risk management, quality by design, corrective actions and preventive actions, process capability analysis, Six Sigma, process analytical technology, lean manufacturing, total quality management, ISO series and HACCP.

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Results: Upon reviewing the previously highlighted guidelines and the practices that are widely applied in the pharmaceutical industry, it was noticed that there is an abundant number of papers and articles that explain the general guidelines and practices but the literature lack those describing application; case studies of the pharmaceutical factories applying those guidelines and significance of those guidelines and practices.

Conclusions: It is recommended that the literature would invest more in the area of application and significance of guidelines and practices. New case studies should be done to prove the feasibility of such practices.

Contents

1. Introduction

The quality in the pharmaceutical industry has become a very important topic. Since the world has gathered together to harmonize its practices and guides and the launching of the FDA current good manufacturing practices – the cGMP; for the 21st century – there has been a growing awareness for the significance of the quality of the pharmaceutical products (Woodcock, 2004). This awareness is represented through the appearance of several definitions defining exactly what the quality of the medicine should be (LEE and Webb, 2009). Many articles were written to demonstrate the special nature of the product-customer relationship of medicine and patients (Woodcock, 2004). Also the important role of governments was emphasized through the joint statement between the international pharmaceutical federation; FIP; and the international federation of pharmaceutical manufacturers associations; IFPMA; to ensure the safety of medicinal products in order to protect the patient (FIP Council, 1999), providing that the pharmaceutical industry is one of the most closely regulated industries for more than 50 years (Woodcock, 2004).

Since 2002, FDA began an initiative to address cGMP for the 21st century (Woodcock, 2004). This effort involved taking new looks at both the regulatory and industrial systems for insuring drug quality (Larson, 2006).

A literature review was conducted on the quality in the pharmaceutical industry, identifying 102 publications that focus on conceptual issues, methodological issues, or the application of different practices and/or guidelines applied in the pharmaceutical industries. The content of these sources was analyzed, and a number of themes were identified.

The literature review has two objectives concerned with the quality guidelines and practices of the pharmaceutical industry and the organization such as practices and guidelines to make a guide for others to use.

A research of this kind serves to integrate past research and can help current and future researchers, and practitioners employing the suitable guideline or practice to develop their methodological decisions in upgrading the industry.

This article introduced some issues regarding what is so special about pharmaceutical quality and different drivers of quality are then identified (Fraser, 2005; Dean and Bruttin, 2001). This is followed by the identified research themes and

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their development. Finally, managerial implications are discussed.

2. Methods

A search was made of the following databases: WHO, FDA, ICH, and EU to download their corresponding guidelines. Using the Google search engine; also a number of papers and articles were downloaded. Search words used were: pharmaceutical quality, quality and pharmaceutical industry. Papers that were not academic in nature were rejected (for example, those that did not provide reference citations).

The final sample consisted of 102 publications; 56 publications were related to the pharmaceutical quality directly while 46 publications were concerned with the general quality practices.

Two research themes could be identified in the articles studied in this literature review.

They included:

- Guidelines of the pharmaceutical quality.
- General practices recently applied in the pharmaceutical industry.

For each of these research themes the authors synthesize the main findings and offer suggestions for further research.

2.1. Research theme 1: guidelines of the pharmaceutical quality

The most important guidelines that are widely applied in the pharmaceutical industry are:

2.1.1. WHO guidelines

WHO has published a handbook on the GMP in particular, entitled: Quality assurance of pharmaceuticals, a compendium of guidelines and related materials, Volume 2: good manufacturing practices and inspection (Quality Assurance of Pharmaceuticals, 2004).

It consists of 4 chapters:

Chapter 1: WHO GMP: main principles for pharmaceutical products.
Chapter 2: Good manufacturing practices: starting materials.
Chapter 3: Good manufacturing practices: specific pharmaceutical products.
Chapter 4: Inspection.

And 7 annexes:

Annex 3: Radiopharmaceutical products.
Annex 4: Good manufacturing practices for pharmaceutical products: main principles.
Annex 5: Model Certificate of GMP.
Annex 6: Sterile pharmaceutical products.
Annex 6: Guidance on GMP inspection.
Annex 7: Pre-approval inspection.
Annex 8: Quality system requirements for national GMP inspectorates.

2.1.2. FDA guidelines

Pharmaceutical manufacturers have just begun to understand and apply the FDA's cGMPs for the 21st century: A Risk-Based Approach; the initiative outlines immediate, near and longer-term stages that FDA believes will take two years to be implemented (Larson 2004).

On the technical side, FDA states three concepts that will guide the reevaluation process: advances in risk management science, advances in quality management science and advances in pharmaceutical science and manufacturing technology (Larson, 2004).

The most important guidelines are Code of Federal Regulation 210, 211.

21CFR Part 210: 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 to assure that such a 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 claims to possess.

21CFR Part 211: The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

The FDA has concluded that modern quality systems together with manufacturing processes and product knowledge, can handle many types of changes to facilities, equipment and processes without the need for regulatory submission (Fraser, 2005).

2.1.3. EU guidelines

The core of European Union legislation in the pharmaceutical sector is gathered in Volume 1 and Volume 5 of the publication; "The rules governing medicinal products in the European Union".

- Volume 1 – EU pharmaceutical legislation for medicinal products for human use.
- Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use.

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 – Notice to applicants and regulatory guidelines for medicinal products for human use.
- Volume 3 – Scientific guidelines for medicinal products for human use.
- Volume 4 – Guidelines for good manufacturing practices for medicinal products for human and veterinary use.
- Volume 6 – Notice to applicants and regulatory guidelines for medicinal products for veterinary use.
- Volume 7 – Scientific guidelines for medicinal products for veterinary use.
- Volume 8 – Maximum residue limits.
- Volume 9 – Guidelines for pharmacovigilance for medicinal products for human and veterinary use.
- Volume 10 – Guidelines for clinical trial.

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2.1.4. ICH guidelines

The International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) is a special project that gathers the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three different regions; to discuss scientific and technical aspects of product registration.

The objective of such harmonization is a more efficient use of human, animal and material resources, and the removal of any delay that is not essential in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

2.2. Research theme 2: general practices recently applied in the pharmaceutical industry

2.2.1. Quality risk management

All products and all processes have an inherent element of risk (Griffith, 2004).

In an organization that is intending to apply an effective quality risk management approach, a clear definition of what is considered ''risk'' should be agreed upon because of the too many stakeholders in the pharmaceutical industry and their corresponding diverse interests (ICH Q9, 2003).

The FDA has noticed that it needs to reorganize its procedures and processes to merge the use of risk management programs (RMP) within the agency and within the industries it regulates. Consequently, the FDA has started publishing position papers and guidelines on what it expects to see in an RMP (Griffith, 2004).

Risk management plans should be used to identify risk (Griffith 2004).

Quality Risk Management is defined as a method for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product through the product lifecycle where decisions can occur at any point in the process (ICH Q9, 2003).

In the guideline entitled Medical Device Use-Safety: incorporating human factors engineering into risk management; it clarifies how hazards related to medical device use should be directed during device development as part of the risk management process (CDRH, 2000).

2.2.2. Quality by design

ICH Q8 defines design space from the concept that quality cannot be tested into product but has to be built in by design (ICH Q8, 2005–2008).

Based on the ICH Q8; which concerns pharmaceutical development with targeting designing quality into the ingredients, formulation and manufacturing process to deliver the intended performance of the product. Design space is presented by the applicant and is subject to regulatory assessment and approval (ICH Q8, 2005–2008).

In these situations, opportunities exist to develop more flexible regulatory approaches.

The design and conduct of pharmaceutical development research should be consistent with their intended scientific purpose (ICH Q8, 2005–2008).

2.2.3. Corrective action and preventive actions

QMS nonconformities and other system deficiencies, including legal noncompliance, should be analyzed to detect patterns or trends. Identifying trends allows the manufacturer to anticipate and prevent future problems (EPA, 2009).

The organization should focus on correcting and preventing problems. Preventing problems is generally cheaper than fixing them after they occur. The organization should also start thinking about problems as opportunities to improve (EPA, 2009).

''Root cause analysis'' is a process by which the manufacturer can identify causes and preventive actions (EPA, 2009).

In general, CAPA experts recommend that root-cause investigations follow a four-step process (Bartholomew, 2006):

- *Identify* the problem.
- *Evaluate* its magnitude, which includes assessing risk.
- *Investigate* and assign responsibility.
- *Analyze* and document the root cause of the problem.

For example a new corrective action tracking system had helped Alcon Laboratories Inc. unite its many corrective and preventive action systems worldwide resulting in faster time of closure on corrective action, both access and speed to information are much greater and finally quality professionals are able to focus on more important issues (Davis, 2003).

2.2.4. Process capability analysis

Process capability is the comparison of the ''Voice of the Customer'' (VOC) with the ''Voice of the Process'' (VOP). VOC, which is built on customer requirements, is defined by the specification limits of the process, which are fixed, while VOP is defined by control limits, which are based on performance data and vary over time (Tarpley, 2004).

Metrics such as capability index namely Cp and Cpk were developed several years ago to calculate this comparison between control and specification limits (Tarpley, 2004).

The capability index a ratio that compares process spread to tolerance spread and results in a single number. It is a management tool which is used to compare process performance (Ruth II, 2005).

2.2.5. Six Sigma

Harry and Schroeder (2000) define Six Sigma as ''...a business process that enables companies to increase profits dramatically by streamlining operations, improving quality, and eliminating defects or mistakes in everything a company does....'' It can help an organization reduce defects and improve profitability using several basic tenets (Harry and Schroeder, 2000; Johnson and Swisher, 2003; Pande et al., 2000; Williams 2003; Goeke and Offodile, 2005)

Six Sigma Projects are based on the DMAIC model (Stamatis, 2002).

The DMAIC model is the generic model of six sigma methodology. It is an acronym that stands for; Define, Measure, Analyze, Improve and Control. Sometimes this model includes recognize as an awareness item to the model. Each of the components addresses a different aspect of the overall improvement and breakthrough strategy (Stamatis, 2002).

The pharmaceutical industry sigma level is from 2 to 3; this results in a 25–35% defects (Hussain, 2005).

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An example of the pharmaceutical firms that adopted the methodology of Six Sigma is AstraZeneca where the operations and quality staff were trained to apply DMAIC principles every day, to measure and improve performance through cross-functional "continuous improvement" (CI) teams (Shanley, 2005). Two years ago, at Westborough, Massachusetts, cross-functional CI teams involving QA, engineering and operations applied DMAIC principles to solve a major capacity problem for a key product. The teams discovered wasteful processes, effectively adding 20 million extra units of capacity per year. Where a capital investment of less than $100,000 led to $60 million to $70 million in revenue gains, without hiring new staff as Ron Matthews, vice president of manufacturing and supply chain at the company, said (Shanley, 2005).

2.2.6. Process analytical technologies

Process analytical technologies (PAT); play a key role in enabling "quality by design" and scientific aspect of manufacturing. PAT's main aim is to understand and control the manufacturing process through the application of integrated chemical, physical, microbiological, mathematical and risk analysis methods. PAT has been applied in non-Pharma industries for many years, yielding cost savings and manufacturing efficiencies (Fraser, 2005).

The implementation of process analytical technology (PAT) is bringing lots of benefits and improvements for many pharmaceutical processes. The benefits are lower production cycle times, improved manufacturing efficiency, reduced rejects and increased production operating time (Rockwell Automation, 2004).

Within pharmaceutical industry, there have been a number of successful PAT-based comparability protocol submissions, ranging from single-unit operation application at GlaxoSmithKline to a more all-including application covering both drug substance and drug product at Sanofi-Aventis (Shanley, 2005).

2.2.7. Lean manufacturing

Japanese manufacturers re-building after the Second World War were facing declining human, material, and financial resources. These circumstances led to the development of new, lower cost, manufacturing practices. Early Japanese leaders such as the Toyota Motor Company's Eiji Toyoda, Taiichi Ohno, and Shingeo Shingo developed a disciplined, process-focused production system now known as the "Toyota Production System", or "lean production." The objective of this system was to minimize the consumption of resources that added no value to a product (Womack et al., 1990).

Lean manufacturing is about eliminating waste across an entire company and focusing on the big picture through learning how to do more with less (Nystuen, 2002).

Lean means putting the right things in the right place at the right time the first time while minimizing waste and being open to change. This leads to less waste, less design time, fewer organizational layers, and fewer suppliers with more employee empowerment, more flexibility and capability, more productivity, more customer satisfaction and without a doubt, more long-term competitive success. Lean principles incorporated in the workplace today can spell business survival for the future (Nave, 2002).

In AstraZeneca; rather than being submerged into Lean, the company launched a limited initiative at its global facilities in 2002 which is the Pull Manufacturing; this initiative required that the company's manufacturing teams shift their focus from output to customer alignment and service. Also, the initiative has lead to reduction in the cycle time. In one case, it allowed lead time for a key $1.5-billion-per year product to be reduced by 25% during a period when demand for the drug was increasing by 30% (Shanley, 2005) (see Table 1).

Table 1 ICH categories and main topics.

Q: Quality Topics
Those relating to chemical and pharmaceutical Quality Assurance:

(1) Stability
(2) Analytical Validation
(3) Impurities
(4) Pharmacopoeias
(5) Quality of Biotechnological Products
(6) Specifications
(7) Good Manufacturing Practice
(8) Pharmaceutical Development
(9) Risk Management

E: Efficiency Topics
Those relating to clinical studies in human subject

(1) Clinical Safety
(2) Clinical Study Reports
(3) Dose-Response Studies
(4) Ethnic Factors
(5) Good Clinical Practice
(6) Clinical Trials
(7) Guidelines for Clinical Evaluation by Therapeutic Category
(8) Clinical Evaluation

S: Safety Topics

(1) Those relating to *in vitro* and *in vivo* pre-clinical studies
(2) Carcinogenicity Studies
(3) Genotoxicity Studies
(4) Toxicokinetics and Pharmacokinetics
(5) Toxicity Testing
(6) Reproductive Toxicology
(7) Biotechnological Products
(8) Pharmacology Studies
(9) Immuno-toxicology Studies
(10) Joint Safety/Efficacy (Multidisciplinary) Topic

M: Multidisciplinary Topics
They are Cross-cutting topics, which do not fit uniquely into one of the above categories.

- M1: Medical Terminology (MedDRA)*
- M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)
- M3: Timing of Pre-clinical Studies in Relation to Clinical Trials
- M4: The Common Technical Document (CTD)
- M5: Data Elements and Standards for Drug Dictionaries

* Medical Dictionary for Regulatory Activities Terminology.

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Table 2 The cost of system improvements in Lilly.

Control system improvement	% Of savings gained	% Of overall cost of control system
Implementation of regulatory control systems and basic hardware	20	70
The use of advanced control procedures such as feed forward and model based	75	80
The application of optimization methods to the process	100	100

Eli Lilly had suffered factory losses – process barely capable with some nonconformance and variability in product quality, the application of lean lead to system improvement and cost savings as shown in the following Table 2 (Mohan, 2006).

2.2.8. Total quality management

Total quality management (TQM) is a concept rather than a technique. It is a philosophy that stresses a systematic, integrated, and consistent perspective that would involve everyone and everything in the organization (Isaac et al., 2004).

TQM is a management philosophy that builds a customer driven, learning organization that is devoted to the total customer satisfaction through continuous improvement in the effectiveness and efficiency of the organization and its corresponding processes (Corrigan, 1995).

TQM is widely known for improving quality and other performances such as productivity, profit, market share, and competitive edge of organizations of various types (Sun, 2000; Isaac et al., 2004).

2.2.9. ISO series

ISO 9000 series: ISO 9000 is concerned with ''quality management''. This means what the organization does to increase customer satisfaction through meeting customer and regulatory requirements and continually improving its performance (ISO 9000 and 14001 in brief, 2009).

ISO 14000: ISO 14000 is an environmental management system, describes the requirements for an organization's environmental management system and can be used for certification/registration and/or self declaration of an organization's environmental management system (ISO 14001, 2004).

This means what the organization does to (ISO 9000 and 14001 in brief, 2009):

- Minimize harmful effects on the environment caused by its activities.
- Achieve continual improvement of its environmental performance.

ISO 17025: It gives the general requirements for the competence of testing and calibration laboratories (ISO/IEC 17025, 2005).

A specific version of this standard for Medical Laboratories has been developed; ISO 15189:2003 then ISO 15189, 2007 was published on 19th April 2007 (ISO 15189, 2007).

Through the accreditation process; the testing laboratory reaches the status of an independent institution (Mettler-Toledo GmbH, 2003).

2.2.10. HACCP

The Hazard Analysis and Critical Control Point (HACCP) methodology was known to be a safety management system used in the food industry. Their main aim is to prevent known hazards and to reduce the risks that they will cause at specific points in the food chain (Annex 7; WHO TRS No. 908, 2003).

Procedures, including GMP, address operational conditions and provide the basis for HACCP. HACCP is a systematic method for the identification, assessment and control of safety hazards. The hazards are classified as biological, chemical, or physical agents or operations that might cause illness or injury if not controlled. In the manufacture of pharmaceuticals, this includes the manufacture of certain antibiotics, hormones, cytotoxic substances or other highly active pharmaceuticals. Together with operations such as fluid bed drying, granulation is an example of hazard unit operations. The use of inflammable solvents (solutions) and certain laboratory operations may also produce hazards (Annex 7; WHO TRS No. 908, 2003).

The HACCP system is based on seven principles (Annex 7; WHO TRS No. 908, 2003):

- Conduct a hazard analysis.
- Determine the critical control points (CCPs).
- Establish target levels and critical limit(s).
- Establish a system to monitor the CCPs.
- Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
- Establish procedures to verify that the HACCP system is working effectively.
- Establish documentation concerning all procedures and keep records appropriate to these principles and their application.

3. Results

Upon reviewing the previously highlighted guidelines and the practices that are widely applied in the pharmaceutical industry, it was noticed that there is an abundant number of papers and articles that explain the general guidelines and practices but the literature lack those describing application; case studies of the pharmaceutical factories applying those guidelines and significance of those guidelines and practices.

4. Discussions

It is recommended that the literature would invest more in the area of application and significance of guidelines and practices.

Also, there are some new practices that are recently applied to the pharmaceutical industry though they are widely applied in non pharmaceutical industries, such as: the lean manufacturing; the Six Sigma; the total quality management. Both managers at the pharmaceutical industry and literature should focus on the adoption of such practices into the pharmaceutical industry making use of the previous research in the

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non-pharmaceutical industry application. New case studies should be done to prove the feasibility of such practices.

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