Good Manufacturing Practices (GMP): "Planning for Quality and Control in Microbiology"

5

Upendra Krishnalal Jani

Abstract

Good manufacturing practices with comprehensive design and proper implementation of the quality system infrastructure helps manufacturer to achieve quality objectives. Quality assurance covers various aspects of manufacturing and quality control process which ensures that products are manufactured consistently as per the quality standards. Quality assurance integrates cGMP and quality control along with environmental monitoring and occupational health and safety hazards. To implement quality management system effectively, manufacturer must have instructions, processes, and adequate resources relevant to the need of product. Monitoring and controlling the QMS not only measures the effectiveness, but helps for the continuous improvement. cGMP gives consumers a confidence that products are meeting required standards for release and safe for intended use. Compliance with basic requirements of cGMP elements ensures/assures that products have achieved quality attributes during manufacturing cycle. Quality assurance is the responsibility of all personnel engaged for the manufacturing and control within the organization.

Keywords

Good Manufacturing Practices • Quality Assurance • Quality Control • Environmental Monitoring Quality Management System • Proactive Compliance Approach

5.1 Introduction

During aseptic manufacturing of biologics, sound process, equipment, and proper facility design is used to minimize/eliminate contaminants. Monitoring such important means and infrastructure, one can measure the effectiveness of

U.K. Jani (✉)
Hester Biosciences Limited, Ahmedabad, Gujarat, India
e-mail: upendra.jani@hester.in

P. Shukla (ed.), *Frontier Discoveries and Innovations in Interdisciplinary Microbiology*,
DOI 10.1007/978-81-322-2610-9_5

contamination control. With trend analysis, identification of threats to the purity of the product can be taken care to build quality products. cGMP is a set of scientifically proven sound methods, practices, or principles that are implemented and documented during research and development of the product and during commercial manufacturing. cGMP regulations establish minimum requirements for methods, controls, and protocols. Its implementation during manufacturing process religiously assures product quality attributes for their intended use when marketed.

5.2 Basics of cGMP

5.2.1 Quality Assurance

QA usually (a) reviews and approves all standard operating procedures (*SOPs*) related to production, quality control, and maintenance; (b) reviews batch manufacturing and test records; (c) performs self-audits; (d) performs annual product quality reviews (*APQR*); (e) evaluates trend analysis; and (f) ensures system control, consistency, and validation. QA ensures that products are made in accordance with manufacturing standards and meets their predetermined specifications (World Health Organization 2013a). Good manufacturing practices (GMP) is based on science- and risk-based approaches (World Health Organization 2010, 2011; Lynn 2013). Quality assurance along with quality control is a part of the broader concept of quality management. QA is often explained by the "plan, do, check, act" (PDCA) cycle.

5.2.2 Production and Process Controls

Written standard operating procedures for manufacturing and quality control shall be followed and documented while performing the activity. Any change/variation from these procedures shall be recorded and justified with proper explanation. Maintenance is coordinated for the preventive/planned maintenance. Calibrations and validations are followed as per the validation master plan (*VMP*) for the critical equipment, systems, and processes (Process Validation 2012; U.S. Department of Health and Human Services et al. 2011).

5.2.3 Quality Control

QC usually (a) assesses that incoming raw materials, containers, closures, labels, packing materials, in-process materials, and the finished products are suitable for use; (b) evaluates process performance against set standards and limits; and (c) determines acceptance criteria of batch prior to distribution. Quality control is a reactive process which ensures the quality of materials and products, checks for and detects failures, and identifies and corrects the defects. Both QC and production areas should be independent of each other. Dedicated areas required for chemical, biological, and microbiological analysis/testing. Separate instrument room with adequate area with sophisticated instruments should be provided for analysis. Enough storage space with controls is a must to store test samples, retained samples, laboratory reagents, and documents. According to WHO, quality control is the sum of all procedures undertaken to ensure the identity and purity of a finished product. QC ensures the safety and efficacy of a product before it is released for marketing.

5.2.4 Vendor Audit

Audit vendors on a regular basis for the consistent supply of the quality raw materials and packaging materials. The purpose of this audit is also to determine whether the supplier is capable to supply quality material with consistency. It is the responsibility and authority of the quality assurance department to define the relationship and expectations between organization and its supplier for the continuous improvement (Wingate 2014).

5.2.5 Buildings and Facilities

The location, design, and construction should facilitate proper cleaning, maintenance, and operations for the product being manufactured. Adequate space is required for the man-material movement avoiding mix-ups and cross-contamination. The utilities like water, steam, gas, compressed air, and systems such as HVAC should be maintained, qualified, and validated as per the schedule before use (Witcher et al. 2012). Adequate lighting and work environment should be provided. Proper drainage and sewage treatment plant should be provided to meet the regulatory norms. The written procedures for proper sanitation of the facility with sanitation program, where responsibility, schedule, methods, equipment, etc. are mentioned, are a must.

5.2.6 In-Process Testing

One must have written procedures for (a) testing of product while being manufactured and (b) monitoring aseptic environment to assure batch sterility, uniformity, and integrity.

5.2.7 Laboratory Controls

For each batch produced, QC tests the product for the compliance with the finished product specifications as guided by the regulatory requirements before release (Sandle 2010). A final release approval is given by quality assurance for the distribution in the market.

5.2.8 Expiry Date

Results of the stability testing of the product at defined time, temperature conditions mentioned in the pharmacopoeias, determine the expiry date. It assures that product meets applicable standards as per the label claim.

5.2.9 Packaging and Labeling

Correct and released labels and packaging materials should be used as specified in the written procedure. Reconciliation of labels and packaging material is a must. It helps to control mix-ups and recalls.

5.2.10 Stability Testing

A well-designed "stability testing program" shall be followed to determine storage conditions and expiry date (CFR 211.22). Trending stability test results help to monitor/control acceptance criteria and consistency of production. It's a key element and essential part for new drug development program in R&D. Stability test results help to decide storage conditions and shelf life.

5.2.11 Production Record Review

Batch manufacturing records and QC test records shall be reviewed and approved against established standards/acceptance criteria of master formula record (*MFR*) for the compliance before release/distribution in the market.

5.2.12 Deviation Investigations

Sometimes certain unplanned departures from QA written specifications may occur. If such deviations do not affect the quality and safety of the product adversely and one decides to accept such material/product under deviation, a written procedure should be established. This procedure is applicable to all raw materials, packaging materials, and semifinished and finished products. No deviation is permitted from pharmacopoeial and statutory requirements. Some examples of deviations include: production, EHS, quality improvement, audit, customer service, technical, material complaint, and system routing deviations (US Food and Drug Administration 2006).

5.2.13 Complaints

A written procedure for handling of all written and oral complaints is required. Complaints are handled through proper route – from field to manufacturer via quality assurance department. Quality control checks/tests their retained samples with respective batch. Results are conveyed to the complainant in the form of report with findings/justification. Reports are retained for 2 years after expiry of the said batch.

5.2.14 Records and Reports

Documentation of various records and reports is essential for the review and trend analysis. The review of validation reports, out of specification (*OOS*) results, FDA inspection report, and deviation reports is a must. Customer feedbacks shall be analyzed for quality improvement. Robust effective "recall" procedure is required.

5.2.15 Self-Inspection/Self-Audit

The company shall carry out self-inspection with the help of experienced team members within the organization on a regular time interval. Members with the adequate resources and authority should focus on globally harmonized regulatory standards (Harmonized Tripartite Guideline 2008, 2009). Nonconformities are discussed among the senior officials, and corrective/preventive actions are taken. The audits shall be conducted periodically, the frequency and the depth of audit being influenced by factors such as urgency and focus at a given point and a given situation. Audit checklist shall be drawn by quality assurance, in consultation with, but not necessarily under directions from, persons responsible for specific activities which the audit intends to cover.

5.2.16 Training

The deficiency-related training includes new employee orientation, process redesigns, SOP revision, and technical training (Welty 2009). The company shall train all the personnel (production, quality control, and maintenance) as per the "annual training plan." Training updates the knowledge of the employees regarding cGMP concepts and revisions/amendments. Training need is identified and adequate resources either internal or external should be provided. There are two basic needs for training in pharmaceutical companies:

- Extend quality training to all departments
- Perform specific departmental training in each functional area

5.3 Environmental Monitoring

A *clean room* is a controlled environment where products are manufactured aseptically (International Organization for Standardization 1999). It has a controlled level of contamination specified by the numbers of particles per cubic meter with a defined particle size. It must be designed, qualified, and operated according to the international regulatory standards. The layouts/plans with personnel and material flows, air handling systems (HVAC), and utilities (water and gas system) are approved by FDA prior to the commercial manufacturing (WHO 2012). *Contaminants* are generated from *five* basic sources which include: people, facilities, tools, fluids, and product being manufactured. *Contamination* is a process that causes materials or surfaces to be soiled with contaminants. Elimination of such airborne contamination using advanced equipments and technologies required to maintain aseptic environment. People are the major source of contamination in the clean room. Contamination can lead to expensive downtime with increased manufacturing costs. The personnel engaged in manufacturing in aseptic environment should be trained for "clean room behaviors." Environmental monitoring should be conducted using "risk-based approach" (World Health Organization 2013b; Commission Europeenne 2004). The risk associated with cleaning, disinfection, and change over validation and personal health/hygiene activities is

assessed to comply legal requirements mentioned in the cGMP guidelines. A thorough and unbiased investigation which rules out impact on quality, purity, or safety of the product is essential. *W. Edward Deming* has rightly said, "If you can't describe what you are doing as a process, you don't know what you are doing." The precisely monitored and audited "clean room management program" assures that documented procedures and defined protocols are well understood and effectively implemented at all levels within aseptic manufacturing process.

5.4 Quality Management System

Implementing an effective quality management system allows biological manufacturers to meet their ethical and regulatory obligations (Landerville 2014). Adopting a proactive approach to quality management is essential to achieve the step change in quality performance. The critical utilities, equipment, processes, and test methods all need to be validated and controlled appropriately as per validation master plan. Recently, current GMP norms have integrated quality system and risk management approaches. The objective behind such integration was to encourage the industry to adopt modern and innovative technologies. However, after the major revision in GMP regulations (1978), people observed advancements in the manufacturing science, technology, and understanding regarding quality systems. The ultimate aim of the cGMP regulation is to provide flexibility. It depends upon the type of business; however, they are very similar and share essential elements.

5.5 The Concepts of Modern QMS

The concepts of modern QMS focus on the quality product. Quality in totality comprises established strength, identity, and purity. The manufacturer must develop the product in such a manner that the finished product with quality attributes is produced with consistency.

5.5.1 Quality by Design (QbD)

QbD provides sound framework for transferring the technology from development stage in R&D to scale-up level for the commercial production. This knowledge and process understanding helps to resolve post-development changes and optimization, if any.

5.5.2 Quality Risk Management

It is an essential part of QMS. It helps to establish specifications, process parameters, and acceptance criteria. Assessment helps to mitigate the changes to process or specifications and determines the corrective and preventive actions after successful investigations (Harmonized Tripartite Guideline 2005).

5.5.3 Risk Management

Quality is the science of identifying and controlling variations. Risk management is the future of quality management. It is an ongoing cyclical process. It should enable control or elimination of significant risks as well as the identification of any new risks and processes. Risk management aims to be proactive approach once embedded in an organization. Risk reduction measures will be preventive actions rather than corrections or corrective actions.

5.5.4 CAPA

It is an integral part of QMS with other system-like deviation management, handling of out of specification (OOS), and change control procedure. The successfully implemented CAPA procedure helps to handle failures, nonconformances, and deviations.

Some advantages are:

- Prevents recurrence if applied effectively.
- Provides a structured plan to address identified issues.

- Provides for continuous improvement and effective use may result in proactive actions being taken.
- Provides a record.

Some disadvantages are:

- Retrospective for correction and corrective actions.
- Not a standalone tool.
- Training and knowledge are required to apply effectively and understand the differences between correction and corrective and preventive action.
- Requires established standards and controls for a baseline to be set.

5.5.5 Change Control

It is another cGMP tool, which focuses on how to manage and control unintended issues during aseptic manufacturing of biologics. The changes that alter specifications, or critical attributes, require regulatory approvals. It creates an environment which encourages continual improvement following change control.

5.5.6 Six-System Inspection Model

It is a system-based approach, where quality system is integrated with production, facilities and equipment, laboratory controls, materials, and packaging and labeling to help manufacturer to keep systems under control to meet the regulatory compliances.

5.6 Proactive Compliance Approach

It was rightly said by *John Ruskin*, "Quality is never an accident; it is always the result of intelligent effort." A collective challenge facing the industry is to achieve *proactive compliance.* This involves effective management and control of the manufacturing environment to avoid problems rather than just responding to problems after they have happened. The fundamentals of quality and compliance must never be compromised. Today's modern businesses are becoming more proactive and less reactive. Quality assurance involves taking a proactive approach to ensure drug products are made in accordance with manufacturing standards and met their predefined product specifications (Wright 2012a). The aim is for quality and compliance to be achieved *right the first time* rather than depend on detecting problems. The aim is to continually improve manufacturing standards, eliminating errors along the way. A holistic approach to quality assurance is needed. The internal control framework needs to cover governance, systems, and processes, as well as distinct activities that encourage supportive mindset and organizational behavior. The holistic approach to quality assurance needs to promote transparency in support of performance improvement. An open and trusting relationship must be maintained so that production problems are raised as they occur for rapid resolution. A learning culture needs to replace a *mistakes-are-punished* or a *someone-is-to-blame* approach to quality issues (Wright 2012b). Quality can be better managed when it is recognized and understood that the control of variability and prevention of waste are imperative to achieve a cost-effective business. Ideally, we strive to keep quality, cost, and supply in harmony, but when we need to prioritize, it is only possible to achieve two, and quality must always be preserved. Quality management when structured with quality assurance using cost analysis as a business driver reaps the cost benefits of a proactive approach. Shared beliefs, values, attitudes, and behavior patterns are pieces of the jigsaw that must come together. The energy and motivation for quality comes from the top. The management must acknowledge the challenge of change in their organizations and stay vigilant. A culture of quality will empower teams to continually improve and solve the problems (Gallant 2014). We must remember that the person at the end of our supply chain is depending on us to provide safe and effective products. Better real-time data presents more meaningful information, con-

tributing to a better knowledge and understanding of the process, an increase in product quality, and a safer product. Improved yields, cost savings, and increase profits will be the result. A knowledge update on clean rooms, associated air management elements, and other accessories is the need of the era.

References

CFR 211.22(a), Responsibilities of quality control unit, Sub part B – organization and personnel, Ch. 1, vol 4, pp 144

Commission Europeenne (2004) Good manufacturing practice, annex 1: manufacture of sterile medicinal products. Bruxelles, bio contamination control (ISO 14698). International Organization for Standardization, Geneva

Gallant J (2014) The road to a culture of quality [Article]. Pharmaceutical Online, 19 Sept 2014

Guideline on Process Validation, 29 Mar 2012 EMA/CHMP/CVMP/QP/70278, Rev 1

ICH Harmonized Tripartite Guideline (2005) Quality risk management, Q9, Current step 4 version dated 9 Nov 2005

ICH Harmonized Tripartite Guideline (2008) Pharmaceutical quality system, Q10, Current step 4 version dated 4 June 2008

ICH Harmonized Tripartite Guideline (2009) Pharmaceutical development Q8 (R2), Current step 4 version dated Aug 2009

International Organization for Standardization (1999) Clean rooms and associated controlled environments (ISO 14644). International Organization for Standardization, Geneva

Landerville T (2014) Quality management systems guide. Isocert Solutions, Santa Rosa

Lynn S (2013) Product manufacturing and manufacturing practices (CGMPs). USFDA, 13 Oct 2013

Sandle T (2010) Best practices in microbiology laboratory training. In: Hodges N, Hanlon G (eds) Industrial pharmaceutical microbiology: standards and controls. Euromed, Basingstoke, pp S11.1–S11.16, Supplement 11

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicines (CVM) (2011) Guidance for industry, process validation: general principles and practices. Current Good Manufacturing Practices (CGMP) revision 1, Jan 2011

US Food and Drug Administration (2006) Guidance for an industry: quality systems approach to pharmaceutical CGMP regulations. US Department of Health and Human Services, Rockville

Welty G (2009) Developing a continuing CGMP training program. J GXP Compliance 13(4):86–96

WHO (2012) Environmental monitoring of clean rooms in vaccine manufacturing facilities- points to consider for manufacturers of human vaccines. WHO, Geneva

Wingate G (2014) Moving from quality control to quality assurance. Pharm Eng 34:2

Witcher MF et al (2012) Biopharmaceutical manufacturing in the twenty-first century: the next generation manufacturing facility. Pharm Eng 32(2):10–22

World Health Organization (2010) Good manufacturing practices for sterile pharmaceutical preparations. In: WHO expert committee on specifications for pharmaceuticals preparations. Forty-fourth reports, vol 957, WHO technical report series. World Health Organization, Geneva, Annex 4

World Health Organization (2011) WHO good manufacturing practices: main principles for pharmaceutical products. In: WHO expert committee on specifications for pharmaceutical preparations. Forty-fifth report, vol 961, WHO technical report series. World Health Organization, Geneva, Annex 3

World Health Organization (2013a) Quality assurance of pharmaceuticals WHO guidelines, related guidance and GxP training materials. World Health Organization, Geneva

World Health Organization (2013b) WHO guidelines on quality risk management. In: WHO expert committee on specifications for pharmaceutical preparations. Forty-seventh report, vol 981, WHO technical report series. World Health Organization, Geneva, Annex 2

Wright R (2012a) How to take charge of your manufacturing process [Magazine Article]. Pharmaceutical Online, 29 Nov 2012

Wright R (2012b) How to create an innovative culture in a pharma company [Magazine Article]. Pharmaceutical Online, 1 June 2012