



QUALITY MANAGEMENT OF A GMP LABORATORY FOR HUMAN CELL AND TISSUE THERAPY: OUR EXPERIENCE IN UKM MEDICAL CENTRE

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ABSTRACT

Good Manufacturing Practice (GMP) helps to ensure the quality, safety and efficacy of a manufactured medical product. The Quality Management System is an essential part of a GMP facility as it oversees and ensures that the manufacturing process and facility are controlled and maintained in good condition in order to produce quality products. To ensure that all processes adhere to our quality standard, standard operation procedures (SOP) have been developed so that all processes and procedures are defined clearly and unambiguously, and all results documented to allow traceability. Starting material in the production must be of certain quality and all patient samples must be free from infectious diseases to protect the operators as well as to prevent cross-contamination among samples. When new processes, equipment or materials are introduced into the already established facility, validations must be performed to assess their suitability. The GMP regulation also requires that all deviations from the standard operating procedures be documented and investigated accordingly to correct and prevent them from occurring again. Personnel must be trained and assessed accordingly before they are allowed to carry out certain task and be able to perform their duties with integrity. Cell Tissue Technology (CTT) Laboratory's Quality Management System has been broken up into several sections. Each section encompasses the main components of the Pharmaceutical Inspection Convention/ Scheme (PIC/S) Guide to GMP for Medicinal Products. The objective of this article is to briefly describe the quality management system of our GMP Facility which operates in accordance to the PIC/s Guide to Good Manufacturing Practice and to share our experiences of setting up such a facility.

1.0 Introduction

The Tissue Engineering Centre in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) has recently completed a GMP (Good Manufacturing Practice) facility which consists of 3 clean rooms with supporting anterooms and transition areas. The main purpose of this laboratory (Cell Tissue Technology (CTT) Laboratory) is to provide a means to translate laboratory research to clinical and therapeutic

application in order to improve patient care. Tissue Engineering Centre, UKMMC is involved in many preclinical researches using cells derived products and one of the products which have been trademarked and ready for clinical investigation is MyDerm™, an autologous bilayered human skin substitute which has the potential to treat non-healing diabetic ulcers, burns and trauma injuries.

In order to ensure the safety and quality of this product, activities associated with all stages of the sample collection, processing, testing, storage and release of product, and the training and development of personnel need to be controlled with particular attention given to traceability and quality control of the processes and the products. Standard operating procedures (SOP) need to be developed for each step of the production process and critical control points need to be identified in order to prevent the risk of contamination in the final product. All reagents, materials and devices used in the process shall be evaluated and selected to ensure that they are suitable for clinical applications. If a material can only be used for research and not for clinical application, a risk assessment process shall be performed to minimize the probability of introducing that material into the recipient. [1]. Therefore, in order to fulfill the above requirements, a Quality Management System which operates in accordance to the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE 009-9) was developed. By adhering strictly to this quality system, the products produced by this laboratory shall be of the highest standard and quality.

This article also acts as a supplement to an earlier article published by our colleagues entitled “Process Development for the Production of Human Cell and Tissue in accordance to Good Manufacturing Practice: Our Experience in UKM Medical Centre” [2].

2.0 Regulation and Guidelines: What is GMP?

GMP is an acronym that describes a set of principles and procedures which help to ensure that the products manufactured will have the required quality if the manufacturer adhere to the code of GMP. It can be defined as the quality assurance which ensure products such as foods, drugs, medical devices, cells and tissues are consistently produced and controlled in such a way to meet the quality and safety standards appropriate to their intended use as required by the regulatory authority [3]. A GMP compliant facility will consistently provide a high level of assurance for product quality, safety and efficacy.

In Malaysia, GMP for pharmaceuticals, cosmetics, health supplements and veterinary products are regulated by the National Pharmaceutical Control Bureau (NPCB), Ministry of Health (MoH). According to the Control of Drugs and Cosmetics Regulations 1984, compliance to GMP is a prerequisite for the application of a manufacturing license as well as product registration. On the other hand, GMP for food, industrial chemical products, pesticide and other non-pharmaceutical products are regulated by Department of Standards Malaysia, Ministry of Science Technology and Innovation (MOSTI) [4, 5].

The implementation of GMP as a basic guideline for cell and tissue products has been debated for years. The compromised general guidelines have been drawn by major authority bodies for their respective regions such as Food and Drug Administration (FDA), European Medicines Agency (EMA) and Therapeutic Goods Administration (TGA) Australia which is based on PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE 009-9).

In the emergence of tissue engineering, regenerative medicine and cell therapy products manufacturing in Malaysia, the need for national guideline has also increased. To date, there is no standard guideline to regulate such products locally. CTT Laboratory has adopted the PIC/S Guide to GMP in its facility design, operation, and cell and tissue production. CTT Laboratory has been audited by the NPCB for GMP conformance. It should be able to meet the future and improved international guidelines on cell and tissue therapy products to cater the growing national and regional demand.

3.0 Quality Management

Quality Management is an evaluation of services provided and the results achieved as compared with accepted standards. It can be further broken down into Quality Assurance, Quality Control and Quality Improvement as shown in Figure 1 [6]. Quality Assurance is a set of activities that is designed to ensure that the development and/or maintenance process is adequate to ensure that a system will meet its objectives. It also ensures that the process is defined and appropriate, and the methodologies and standards are developed accordingly. It is an overall management plan to guarantee the integrity of the product. Quality Control is a set of activities designed to evaluate a product and focuses on finding defects in a specific product. It is a process of testing and inspecting to assess the quality of the product [7].



Fig. 1 Quality Control, Quality Assurance and Quality Management

Quality Improvement is the continuous improvement of processes and products. There are many methods available for quality improvement. Among them is the plan-do-check-action or PDCA cycle which has originated from Dr. W. Edwards Deming's lecture in Japan in 1950 [8].

4.0 CTT Quality Management System

The Quality Management System of CTT Laboratory is developed in accordance to the PIC/S Guide to GMP. This guide requires that a facility for the manufacturing of medicinal products be able to produce products that are fit for their intended use, comply with the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy. In order to achieve this quality objective reliably, there must be a comprehensive Quality Management System that is correctly implemented [3].

4.1 Quality System

A quality system is the organizational structure, responsibilities, procedures, instructions, processes and resources for implementing quality management. The quality system should function to ensure that all materials, samples and products are tested and released or rejected based on their quality. It should also ensure the suitability of the facility, the competency of the personnel and that all procedures are in place in order to maintain this quality [3].

In every organization, the reporting structure must be clearly documented. CTT has an organizational chart that is kept updated as staff join or leave the facility. It is made available to all clients, including but not limited to CTT facility staff, research staff, hospital personnel, patients and doctors. Each staff has their respective Job Descriptions to formally define their responsibilities and authorities in the facility. CTT also have a Quality Manual and Site Master File which can be made available upon request and approval from the Quality Manager.

The quality system is reviewed in Management Review Meetings regularly to ensure its continuing suitability, efficiency and adequacy. It will also be evaluated periodically via internal or external audits in order to monitor and improve its health. The audits can be either a System Audit to ensure that the system is in place and meets regulatory requirements or a Compliance Audit to ensure that the facility is following their own system.

A risk management system is in place to identify, assess and mitigate the risk when a product is exposed to potential risks of contamination by agents causing infectious disease transmission, introduction of research grade materials to patients and immunological compatibility complications.

Furthermore, an annual review of the product quality will be conducted to evaluate the consistency of the processes, whether the current specification of the critical material and final product is appropriate and to identify if any processes could be improved.

4.2 Documents & Records

Documents and records are an essential part of GMP. The code of GMP requires written procedures and work instructions for each step of the manufacturing process so that the process follows a defined standard to ensure the quality and safety of the products. Instructions and SOPs are crucial in a laboratory since verbal instructions can be forgotten, misinterpreted or ignored [9]. SOP should be written as detail as practicable so that the instructions and procedures are clear and easy to follow. All critical activities in the laboratory shall be recorded in forms to enable traceability.

All of our documents are stored securely and are accessible to authorized personnel only. We have a system to make documents effective, for training and acknowledgement for each document and for removing old versions of documents from circulation. This process is called document control and is performed by the Quality Department. CTT's document structure is depicted in Figure 2.

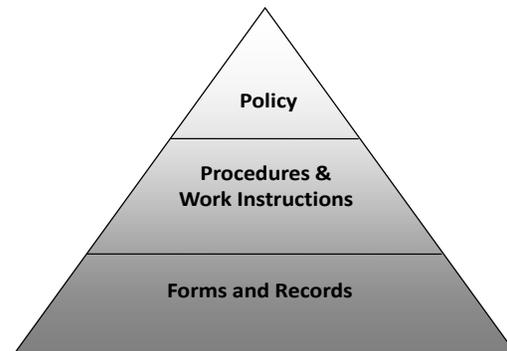


Fig. 2 Cell Tissue Technology Laboratory's Document Structure

4.2.1 Policy

The top tier of the document pyramid is the policy manual. This document defines what will be done and explains why it needs to be done. A quality manual should be written in such a way that it is clear, precise, practical and easy to understand [10]. The "why" can be stated in the quality objectives and the "what" can be included in the mission/vision statement.

4.2.2 Procedure and Work Instructions

The second tier of the pyramid are the standard procedures and work instructions. Standard procedures describe methods

that will be used to implement and perform specific tasks as stated in the policies. The procedures define who should perform the tasks, when the task should be performed and where the documentation will be made showing that the task was performed. Work instructions are usually more detailed and describe a specific task step by step. It can be in form of text, diagram, flow chart, photographs, videos or any format which can be easily understood by the operators. Work instructions explain in simple terms how a task should be carried out [10].

4.2.3 Records

Records are used to document that procedures have been followed and carried out accordingly. Records may be completed forms, a stamp of approval on a product, or a signature and date on a document. Records are used to provide traceability of manufacturing processes for the construction of the final product. They provide data for corrective actions and a way of notifying the recipient's treating physician if the need arises. [10]

4.3 Production & Process Controls

Production operations must follow predefined procedures in order to obtain products of the required quality [3]. All starting materials and samples should be of certain requirements and standards. Critical materials should come with certificate of quality to ensure their suitability to be used in production process. In our laboratory, all patients who are eligible to enroll into the clinical investigation will undergo a routine blood screening for HIV, Hepatitis B, Hepatitis C, syphilis and microbiology test for blood infection. Only samples from patients with negative results will be accepted for further processing. All reagents used in the manufacturing process are recommended to be either clinical or "for further manufacturing" grade in order to produce a final product suitable for clinical use [2]. If no higher grade reagents can be used in place of a research grade reagent, risk assessment shall be performed in order to assess the concentration remaining in the final product and whether they will possess any risk to the patient. Intermediate and final products from our laboratory are also subjected to sterility testing such as mycoplasma, endotoxin, micro-contamination and gram staining before they are released for clinical use.

4.4 Validation

Validation process should be conducted to ensure that any material, process, procedure, activity, system or equipment used can and will reliably achieve the specified results. When new equipment, material or methods are introduced to the established manufacturing procedures, validation should be performed to ensure its suitability. All validation results must

be documented and recorded [1]. Validation studies performed by CTT include process simulation and validation (media fill and dry run), operator aseptic technique validation, transport validation, cleanroom operator capacity validation, label validation, equipment validation, cleaning validation and critical material validation [2].

4.5 Material Control

Starting materials, also known as critical materials, are important in the manufacture of biological products. According to the PIC/S Guide to GMP, critical material must be controlled to ensure that they are purchased from approved suppliers [3]. In CTT, each delivery is inspected for outer and inner packaging integrity, delivery condition (eg. temperature, humidity) and confirmed that the correct order has been delivered. Quality certificates (eg. Certificates of Analysis, Sterility, Conformity, Manufacture etc.) should be acquired before the materials can be released for use. Certain materials such as enzymes and culture media are tested for their specific activity and functionality prior to release for use in the manufacturing process. All critical materials must be stored appropriately after arriving at the facility.

4.6 Occurrence Management

Occurrence management is important to ensure that the facility constantly produces good services and quality products that consistently meet the requirements of the user [11]. During manufacturing processes, many variations could cause deviation from the standard operating procedures that are attributed to human factor, methods, materials, equipment and environment [9]. All deviations from the SOP are referred to as non-conformances and must be documented and investigated accordingly [12]. Occurrence management is also a part of continuous improvement as it aims to correct an event and prevents it from happening again [11].

In CTT, occurrences or incidents are captured in forms of non-conformances, material defects, feedback and complaints. Non-conformance reports (NCR) capture incidents which fail to comply with specified requirements. In NCRs, the root cause of the incident will be identified and proposed corrective and/or preventative actions will be undertaken. When a defect in any critical material used in the collection, testing or product manufacturing is detected, a material defect report (MDR) is used to feedback to the supplier for their further action.

Customer satisfaction also plays an important aspect in a quality management system [11]. Any stakeholder of CTT, including patients, hospitals, clients and staff may generate a customer feedback or complaint. All feedbacks/complaints

will be discussed in the Management Meetings and a response will be given to the complainant as soon as is practical.

5.0 Discussion and Conclusion

CTT's Quality Management System operates in accordance to the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE 009-9). In this article we have shared our experience in the aspects of documentation and records, production and process controls, validation, material control and occurrence management which are a part of our Quality System. Our facility has also been audited by the NPCB and has been confirmed to conform to the requirements of GMP in accordance to the current PIC/S GMP Guides and its relevant Annexes for processing, construct formation and storage of human cells and tissues.

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