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DOCUMENT NUMBER: COMM-QA-068

DOCUMENT TITLE:

Good Manufacturing Practices - GMP - Referred to as Current Good Manufacturing Practices - cGMP

DOCUMENT NOTES:

Document Information

Revision: 05	**Vault:** COMM-QA-rel
Status: Release	**Document Type:** COMM-QA

Date Information

Creation Date: 27 Dec 2018	**Release Date:** 15 Jul 2019
Effective Date: 15 Jul 2019	**Expiration Date:**

Control Information

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Previous Number: COMM-QA-068 Rev 04	**Change Number:** COMM-CCR-087

Good Manufacturing Practices (GMP)

Current Good Manufacturing Practices (cGMP)

- cGMP refers to the Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA).
- cGMPs are minimum requirements. We may implement quality systems and risk management approaches that exceed these minimum standards.

Goals:

1. To understand where cGMP regulations come from, who enforces the regulations and why you need to comply.

2. To gain an understanding of the benefits of compliance with GMP regulations.

What are cGMPs?

- Current Good Manufacturing Practices
- Rules set up by the FDA that drug manufacturers must follow to ensure that a safe and effective product is manufactured
- FDA regulates unrelated, allogeneic hematopoietic stem/progenitor cells as biological products under the Public Health Services Act and as drugs under the Federal Food, Drug, and Cosmetic Act

What is Food Drug and Cosmetic Act?

- A set of laws passed by the U.S. Congress in 1938 giving authority to the Food and Drug Administration (FDA) to oversee the safety of food, drugs, and cosmetics.
  - Replaced Biologics Control Act (1902)
  - Requires demonstration of safety before marketing
  - Site inspections authorized and authorizes the seizure of adulterated or misbranded drugs.

Who interprets and enforces the law?

- The FDA, FDA is an agency within the Department of Health and Human Services and consists of nine Centers and Offices.

Interpretations of the Law

- The Code of Federal Regulations (CFR) is a government publication where federal agencies post regulations based on their interpretation of the law.
- Found in the CFR are the cGMP regulations that relate to the pharmaceutical and biotechnology sector
- Some parts that pertain to CCBB, STCL, Robertson GMP Laboratory:

  -21 CFR Part 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General Part

  -21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals

  -21 CFR Part 600 - Biological Products: General

  -21 CFR Part 11 - Electronic Records; Electronic Signatures

  -21 CFR 1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products

What if cGMPs are not followed?

- "Adulteration"
  - Per the FDA "A drug is deemed to be adulterated if the methods used in or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with cGMP to assure that such drug meets the requirements of this act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess."

Why Comply?

- FDA will perform inspections to ensure adherence to GMPs and the Food Drug and Cosmetic Act.
- Consequences for non-compliance (adulteration) are numerous.

Examples:

- Harm to consumer/public
- Citations / 483 items (citations from FDA are documented on FDA federal form 483)
- Damage to reputation of company/organization
- Product recall
- Closure of facility
- Fines
- Jail

Fundamentals of cGMPs?

- Based on fundamental concepts of Quality Assurance Principles
  - Control
  - Quality, Safety and effectiveness must be designed and built into the product
  - Quality cannot be inspected or tested into a finished product
  - Each step of manufacturing must be controlled to maximize the chances that the finished product will be acceptable

Benefits of cGMPs

- Reduce errors
- Ensure products are safe for humans
- Minimizes variations in potency of product
- Prevents mislabeling and adulteration

Key Parts of cGMPs

- Subpart B – Organization and Personnel
- Subpart C – Buildings and Facilities
- Subpart D – Equipment
- Subpart E – Control of Components and Drug Product Containers and Closures
- Subpart F – Production and Process Controls
- Subpart G – Packaging and Labeling Control
- Subpart H – Holding and Distribution
- Subpart I – Laboratory Controls
- Subpart J – Records and Reports
- Subpart K – Returned and Salvaged Drug Product

Organization and Personnel

- Management Responsibility:
  - Responsible for facility, quality system, organizational structure, ensuring adequate resources
  - Responsible for the actions of those reporting to them
  - Responsible for reviewing products annually; reviewing procedures routinely
  - Responsible for providing adequate resources to perform operations (training, equipment, facilities, personnel)

Quality Unit

- Responsible for Approval or Rejection of:

- All components, raw materials, containers, closures, subassemblies, packaging, labeled finished products, process validation reports, procedures and product specifications.
- Investigative reports for non-conformances and Out of Specifications (OOS).

Quality Unit

- Responsible for reviewing production records and ensuring that any errors have been documented / investigated.
- Responsible for releasing product for use
- Must be independent of manufacturing/operations

Buildings and Facilities

- Buildings must be designed with adequate size and space for operations
- Facilities must be validated
- There must be a good workflow for personnel, materials, products and waste (should flow from clean to dirty to avoid contamination)
- Facility must be easy to clean/sanitize (all surfaces and equipment)
- Environmental controls must be in place (clean rooms etc.)
- Utilities must be validated (water and power supplies etc.)

Buildings and Facilities

- Microorganisms, particles and other hazardous materials must be controlled
- Must have engineering documents that describe the layout of clean rooms (controlled documents)
- Changes to the layout of the room post-validation must be re-validated
- Changes that may impact ventilation must be assessed to determine any impact on microbial levels in the room

Equipment

- Equipment must be qualified (design, installation, operation, performance)
- Equipment must be placed in an appropriate location for proper operation (temperature, humidity, etc.)
- Equipment should be selected based on its intended use and cleanability

Control of Components & Materials

- Suppliers must be evaluated, approved and monitored for quality
- Incoming materials must be tested before they can be accepted for use (certificates of sterility/compliance)
- Materials must be used according to FIFO (First In – First Out)
- Materials must be stored so that they cannot be damaged, mixed or contaminated.

Production/Process Control

- Procedures must be in place and followed
- Should be in a step-by-step format

  Examples:

  - Standard Operating Procedures (SOPs)
  - Work Instructions (Job Aides)

- Deviations must be recorded and justified/resolved

  -Root cause analysis

  -Corrective and preventive action (CAPA)

Packaging and Labeling Control

- Label - A display of written, graphic or printed matter on the package/container of a product.

- Procedures must exist that document receiving, identity, storage, handling, sampling and testing of labels and ensure that integrity is maintained throughout the production and use of the product.

Packaging Control

- Must be examined, sampled, tested and approved before use.
- Packaging cannot be reactive, additive or absorptive
- Packaging should allow for the storage and handling to prevent product contamination and deterioration

Labeling Control

- Must have 100% correctness
- Wording of product labels must be approved by the FDA and cannot be changed without approval.
- Labeling must be inspected prior to release for production application.
- All labels must be reconciled (accounted for).
- Labels must be stored in a manner that physically separates them to avoid mixing/mix-ups.

Holding and Distribution

- Warehousing & Distribution procedures should include:

  - Storage of product under appropriate conditions (temperature, humidity etc.)

  - Quarantine of unreleased or non-conformant product.

  - Traceability/Trackability of product lots/batches

Laboratory Controls

- Written procedures must be established and followed
- All actions must be completed at the time of performance (concurrent work and documentation)
- Calculations must be recorded
- Second person review of records must occur
- Data must be directly recorded into appropriate records (notebooks, database)
- Equipment, software and methods must be validated
- An out-of-specification (OOS) result must be investigated and a root cause identified
- Laboratory data is considered to be a quality record

Records and Reports

- Quality Records are the proof that procedures were followed and they show traceability of product.
- Examples:
  - protocols
  - reports
  - lab notebooks
  - logbooks
  - lot/batch records
  - complaint forms

Quality Records

- Records are legal documents (may be used in a court of law as evidence).
- Signatures on cGMP documentation have the same legal meaning as signatures on contracts.
- Information must be recorded and signed for at the same time of performance on the original record (concurrent documentation).

Personnel

- Must have suitable education, training, and experience.
- Trained in GMPs, job duties, and procedures
- Must wear appropriate clothing and protective apparel
- Must practice good sanitation and not have any illness or open lesions that would affect the safety of the employee or the product.

Record Requirements

- Good Documentation Practices (GDP) used.
- Documentation must be concurrent.
- Details that affect the quality or the effectiveness of the product must be documented and explained to ensure product acceptance.

Good Documentation Practices

- Improper documentation of records is a common root cause of deviations and non-conformance.

- Concise, legible, accurate and traceable records

  - Concise: document tells the entire story and understood by internal/external customers
  - Legible: document must be readable by internal/external customers
  - Accurate: document should be error free
  - Traceable: each aspect of the document must be traceable, such as who recorded it, where and why

Why is good documentation essential?

- Documents are objective evidence that actions or tasks have been performed.
- Helps to reduce regulatory observations that may be raised due to inadequate documentation.

Good Documentation Practices (GDP)

- Ink must be indelible
  - no erasable or water-based inks (no gel pens)
- No correction fluid / white-out
- Write clearly and legibly – avoid abbreviations
- No write-overs or scratching out of entries
- Do not use post-it notes to record data
- Do not pre-enter data (i.e., do not document before doing)

Good Documentation Practices (GDP)

- Fill in all blanks, unless authorized by procedure that an exception is permitted. If unknown or not applicable, use UNK or N/A (date and initial entry).
- Use of ditto marks (" ") is unacceptable.
- If a significant portion of a form is unused, draw one diagonal line across the space and initial/date.

Good Documentation Practices (GDP)

- Employee initials: use at least two initials that will uniquely identify you (e.g., first letter of first and last name).
  - Use the same initials consistently to maintain traceability.
  - If two people have the same initials, use three initials.

Dates and Dating

- A date should include the day, month and year.
- Date format should be consistent.
  - Acceptable formats are: DDMMMYYYY (ex. 07AUG2017) or MMDDYYYY (ex. 08072017)
- Postdating (entering a future date) is not permitted.
- Backdating (entering a previous date) is not permitted. - If it is necessary to document a prior date, an annotation explaining the entry must be recorded dated and initialed. A deviation may also be needed.

How are mistakes corrected?

- Draw a single line through the error
- Make a correction next to the error
- If the reason for the correction is not obvious, write an explanation for the error
- Initial and date the correction

Resources that can be found on the FDA website (www.fda.gov)

- CFR – Code of Federal Regulations Title 21
- Guidance documents published by U.S. FDA.
- Warning Letters from FDA to inspected companies and institutions

Signature Manifest

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All dates and times are in Eastern Time.

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