Basic Understanding of Good Manufacturing Practices Requirements and Execution

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Outline

① To know why GMP
② To know what GMP is
③ To know how to comply with it
④ To know what difficulties will be encountered

Let’s begin….

Why GMP

Why GMP

- …
- …
- …
- Eventually …
  - for Quality
  - …
  - for Total Quality Management (TQM)

Quality is

- "A subjective term for which each person has his or her own definition. In technical usage, quality can have two meanings:

  1. the characteristics of a product or service that bear on its ability to **satisfy stated or implied needs**

  2. a product or service **free of deficiencies**"

[ASQ, American Society for Quality]

TQM is

- Chain Reaction
  - Improve Quality … improve procedure
    improve products / services
    - ↳Decrease Cost … less rework, fewer delay
      less contingency fee
      less cost of warranty
    - ↳Improves Productivity
    - ↳Capture the market with better quality & price
    - ↳**Stay in business**

TQM is [cont]

- Failure driven companies
  - “if it breaks, we’ll service it”
- Quality excellence approach
  - “no defects, no problems, essentially moving toward perfect work processes”

How to comply with quality

- Key elements:
  - Employee involvement
  - Customer satisfaction
  - Continuous improvement
  - …
- Tools:
  - ISO
  - HACCP
  - Six Sigma
  - Control Chart
  - **GMP**
  - …

Why GMP

- Ensure public safety
  - **Identity, Safety, Purity, Efficacy, Potency, Stability, Consistency**
- Achieve top quality pharmaceutical products: free of errors and risks
  - Increase efficiency: ↓ waste, rejects, reworks, complaints & recalls
  - Increase competitiveness
- Regulatory requirement
- Minimum standard for drug manufacturing

Remember …

GMP is a tool

- **to comply with a certain quality level**
- **to help to stay in business**

What GMP is

GMP is

- Good Manufacturing Practices
- Quality System
  - Ensuring products are consistently produced and controlled to the quality standards appropriate to their intended use
  - Ensure that things are done right first time, every time and on time
  - Supported by scientific evidence
- Lifestyle in drug manufacturing

GMP Guidance

- WHO: WHO GMP Guidelines
- Australia: Therapeutic Good Act (TGA)
- USA: Food & Drug Administration (FDA)
- China: GMP Guidance for Pharmaceutical Products
- HK: **GMP Guidelines for Pharmaceutical Products, 1995**

  GMP Guidelines for Proprietary Chinese Medicines, 2003

HK GMP Guidelines 1995

- Part 1: Quality Management in the Drug Industry
  - Section 1: Quality Assurance
  - Section 2: GMP for Pharmaceutical Products
  - Section 3: Quality Control
  - Section 4: Sanitation & Hygiene
  - Section 5: Validation
  - Section 6: Complaints

HK GMP Guidelines 1995 [cont]

- Section 7: Product Recalls
- Section 8: Contract Production and Analysis
- Section 9: Self-inspection & Quality Audit
- Section 10: Personnel
- Section 11: Premises
- Section 12: Equipment
- Section 13: Materials
- Section 14: Documentation

HK GMP Guidelines 1995 [cont]

- Part 2: Good Practices in Production & Quality Control
  - Section 15: Production
  - Section 16: Good Practices in Quality Control

- Part 3: Supplementary Guidelines
  - Section 17: Sterile Pharmaceutical Products
  - Section 18: GMP for Active Pharmaceutical Ingredients

GMP is

1. An appropriate **quality system**
   - encompassing the organizational structure, defined procedures, competent personnel, validated equipment and materials

2. **Systematic actions**
   - building confidence that a product is safe, consistent and reliable

Remember …

GMP diminishing **risks**, inherent in any pharmaceutical production, that cannot be prevented completed through the testing of final products

- **Cross-contamination**
- **Mix-up**

How to comply with GMP

- Organization
- Personnel & Training
- Design & construction Features
- Environment Cleanliness
- Equipment
- Product Components & Vendor Evaluation
- Testing & Re-testing
- Labelling
- Documentation & Recording
- Validation
- Self-Inspection
- …

Organization

- Top management **commitment**
  - Providing resources, personnel, time
- Quality Unit
  - **Separated** from Production Department
  - Having responsibility and authority
    - to approve or reject all procedures or spec.
    - to approve or reject all components, in-process materials, packaging material, labeling and drug products
    - to review production records
    - to investigate and correct any error occurred

Personnel & Training

- Sufficient qualified & competent personnel to carry out all tasks
- Clear job description & responsibility for each key function & personnel
- Authorized Person
  - Responsible for the release of **every** batch of finished products for sales
- Sufficient **training** conducted on a continuing basis and with assessment to assure that employees remain familiar with GMP requirements applicable to them

Design & Construction Features

- Operations performed within specifically defined areas of adequate size
- Construction permit effective **cleaning**, maintenance and proper operations
  - Floors, walls and ceilings of smooth, hard surfaces
  - Temperature and humidity controls
  - Air supply filtered through HEPA filters under positive pressure
- The flow of materials and personnel through the premises designed to **prevent contamination**

Design & Construction Features [cont]

- Separate areas for
  - Materials receiving
  - Materials pending sampling and testing before release for manufacturing or packaging
  - Released components, drug product containers, closures and labeling
  - Rejected components, product containers, closures and labeling before disposition
  - Storage of in-process materials, drug products before releasing (Quarantine), drug product after releasing
  - Different manufacturing process: mixing, packaging, labeling, etc
  - Laboratory operations
  - Rest

Design & Construction Features [cont]

- System for
  - Drains of adequate size, provided with an air break or other mechanical device to prevent backflow
  - Room cleaning and disinfecting
  - Pest controlling
  - Ventilation for air filtration and air exhausting
  - Lighting
  - Environmental monitoring

Environment Cleanliness

- Particles & Microbial
- Controlled by
  - Filtering out particles from the air before it enters the clean areas by using HEPA filters
  - Adequate air flow of at least 10-20 changes per hour
  - Differential pressure between rooms
  - Temperature
  - Relative humidity

Equipment

- Appropriate design to facilitate operations, cleaning and maintenance
- Surfaces that contact components, in-process materials or drug products shall **not** be **reactive**, additive or adsorptive
- Substances required for operation (such as lubricants, coolants, etc.) shall not come into contact with components, drug product containers, in-process materials or drug products

Product Components & Vendor Evaluation

- Containers and closures shall
  - Not be reactive, additive or absorptive
  - Provide protection against foreseeable external factors in storage and use
  - Be clean, and where appropriate, sterilized and processed to remove pyrogens
  - Be specified and tested before use
- Vendor Assessment: Professionalism, Technical Support, Material Quality, Quality System, …

Testing

- Examine each lot of incoming materials before release for use
- Representative sampling from each shipment of each lot shall be collected
- Sample collection precautions:
  - Prevent contamination of contents
  - Use aseptic techniques when needed
  - Identify samples
  - Mark containers which have been sampled

Re-testing

- Retest for identity, strength, quality and purity, as deemed necessary, i.e.,
  - After storage for long periods
  - After exposure to air, heat or other conditions that might have adverse effects

Labelling

- **Identity** labels: for every material and product
  - Quarantine
  - Approved / Released
  - Rejected, Recalled, Returned
  - …
- **Status** labels: for every stage of production
  - Weighing
  - Mixing, Filtration, Filling, Tabletting, Capsulation
  - Cleaning, Sterilization, Disinfection
  - …

Labelling [cont]

- Apparatus / equipment / room status shall be identified:
  - Cleaned / to be cleaned
  - Disinfected / to be disinfected
  - Under maintenance
  - Out of order
  - Validated
  - Calibrated
  - Process in progress

Documentation & Recording

- Establish written procedures to **assure uniformity** from batch to batch
  - Instruction: specification, master formulae, manufacturing, packaging, operation, maintenance…
- Maintain records, including production, control, and distribution, all components (drug product containers, closures and labelling) and disposition of rejected components, …
  - Generally retained for at least 1 year after the expiration date of the batch
- **Control unauthorized copy**
- Critical Documents: Site Master File, Drug/Food Master File, Batch Record, Testing Record, Complaint Record, Recall Record, Distribution Record, Training Record, …

Documentation & Recording [cont]

- Laboratory Record shall include
  - Description of sample
  - Statement of the testing method
  - Statement of weight or measure of sample used for each test
  - All data and test results
  - Initials / signature of individual who performed the test
  - Initials / signature of second person who checked
  - Testing date, approving date

Documentation & Recording [cont]

- Batch Record shall include
  - Product information: name, batch number, registration number, …
  - Each significant manufacturing step
  - Date of each process
  - Identity of individual major equipment and line
  - Identity of components and in-process materials
  - Weights and measures of components used
  - In-process and labeling control records
  - Sampling records and laboratory control results
  - Statement of actual yield
  - Responsible signature: preparing and checking
  - Divergence and investigation (w conclusions and follow-up)

Documentation & Recording [cont]

- Complaint Files shall include
  - Name and strength of drug product
  - Lot number
  - Name of complainant
  - Nature of complaint
  - Reply to complainant
  - Investigation results
  - Lab test results, if any
  - Corrective actions, if any
  - Conclusion
  - Follow-up, if any

Validation

- To **demonstrate reliability** of the process
- To **show** the process **consistency**
- To **build confidence**
- Re-validation

Validation Sequence & Items

- **Validation Master Plan**
- Items include

1. Facility & Utilities (Installation & Operational Qualification)
    - Cleanrooms / Clean Booths
    - Purified Water System / WFI System
    - Stem Generation System
    - Compressed Air System
    - Dust Collection System
    - HVAC System
    - Industrial Steam Generation System
    - …

Validation Sequence & Items [cont]

2. Equipment (Installation, Operational & Performance Qualification)
   - Production Equipment
     - Granulator, Mixer, Drying Oven
     - Tabletting Machine, Encapsulation Machine,
     - Primary Packaging Equipment: Filing, Capping
     - Sterilizer
     - …
   - Testing Equipment
     - Stability Chamber, Spectrophotometer
     - Chromatography: HPLC, GC
     - …

Validation Sequence & Items [cont]

3. Testing Method
    - Accuracy
    - Precision
    - Specificity
    - Detection limit
    - Quantitation limit
    - Linearity and range
    - Ruggedness
    - Robustness

Validation Sequence & Items [cont]

4. Process (Prospective, Concurrent, Retrospective Validation)
    - Solid Dose: Granulation Mixing, Blending, Compression, …
    - Liquid Dose: Mixing, Storage, Filtration, Filling, …
    - Cream: Homogenization, Mixing, Filling, …
    - Cleaning: Visual Inspection, Product Residue, Detergent Residue, …
    - Other Process: Sterilization, Washing, Capping, …

Self-inspection

- To evaluate the system effectiveness
- To re-allocate resources
- To detect the weakness and potential improvement areas, including training needs
- To **develop continuous improvement plan**

Key Elements for GMP Compliance

- Management Commitment
- Organization Structure & Quality System
- Qualified Personnel & Continuous Training
- Facility & Equipment Design & Maintenance
- Components from Qualified Vendor
- Laboratory Testing & Proper Labelling
- Documentation & Recording
- Validation
- Self-Inspection & Continuous Improvement
- …

Common Problems in GMP Execution

Common Problems in GMP Execution

- Organization
  - Lack of commitment
  - Lack of resources for execution
  - …
- Layout & Construction
  - No quarantine area
  - Insufficient environmental monitoring
  - Cracked floor
  - …

Common Problems in GMP Execution [cont]

- Equipment
  - No calibration
  - No performance check of balance before use
  - Rusty
  - Parts not kept improperly

Common Problems in GMP Execution [cont]

- Documentation & Recording
  - No signature; no countercheck
  - Improper correction made, e.g. use of correction fluids
  - No written procedure
  - Incomplete complaint record
  - No up-to-date training record
  - No document review
  - Not legible
  - Not traceable

Common Problems in GMP Execution [cont]

- Personnel
  - Improper gowning
  - No continuous training
  - No training assessment
  - No job description
- Laboratory Testing
  - Poor reference standard keeping
  - Poor data recording
  - Reagent with no label

Common Problems in GMP Execution [cont]

- Labelling
  - Status not defined clearly
  - Poor labelling control
  - Release label not kept securely
  - Inadequate reconciliation of batch label
  - Defective equipment with no label
- Validation
  - Insufficient validation
  - Insufficient raw data
  - No validation programme

Common Problems in GMP Execution [cont]

- Others
  - Dirty apparatus/cleaning tools
  - Fiber shedding towel/mop used for cleaning
  - Rejected materials not segregated
  - Poor disposal handling
  - Fail the principle: “Do what you say”

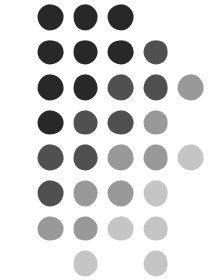
Reaction

1. Establish Quality Policy by top management
2. Design and build proper facilities and equipment
3. Maintain the facilities and equipment
4. Have approved procedures
5. Follow the written procedures
6. Document your work
7. Validate your work
8. Staff Competence (training & experience)
9. Control for quality
10. Audit for compliance
11. …

Keys …

Attitude & Knowledge

More information



- ICH Documents
  - www.ifpma.org/ich1.html

- FDA Documents (21 CFR 11)
  - Parts 210 and 211: Current Good Manufacturing Practices for Finished Pharmaceuticals
  - Part 820: Quality System Regulations
  - www.fda.gov