Workshop For Regulators
On
Revision of Schedule M (GMP)

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Organized by

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Background

- Drugs plays imp role in Public Healthcare
- Drug Regulation to ensure Safety, Efficacy and Quality
- Import, Manufacture, Sale and Distribution of Drugs, Cosmetics and Medical Devices are regulated
- Pharma Industry- Indian public health and also Global health
- All countries are looking at India for Medicines
- Compliance to Schedule M (GMP) is Mandatory

Objective of workshop

- To provide insights to regulators about GMP
- To make aware about new provisions in the revised Schedule M
- To disseminate new provisions to all stakeholders
- To make regulators ready for inspection
- Uniformity in interpretation and implementation

History of GMP

1961	Requirements for equipment and Premises
1986	First amendment based on 1975 WHO guidelines.
2001	Second Amendment based on 1992 WHO GMP guidelines Effective from 11/12/2001 for New Units Effective from 01/01/2004 for Existing Units Extended to another one year
2018	Draft notification G.S.R. 999(E) dated 05.10.2018.

To upgrade and synchronize the Schedule M of the Drugs and Cosmetics Rules, 1945 in compliance with WHO-GMP standards.

Concerns and Challenges

- Multi product manufacturing facilities and loan licensing
- Batches not produced regularly
- Concept of formulation development
- Excipient compatibility studies
- Stability Studies
- Bioavailability/bioequivalence studies
- Quality Culture at all levels
- Continuous training
- Continual improvement in the quality
- Data integrity

Importance of GMP

- All individual units(Tab/Cap/vial etc) not tested before release
- Consumer not able to assess the quality
- Trust and confidence on the regulator
- Consumer don’t have choice of medicine (Manufacturer)
- Low and high dose harm to the consumer
- Affects economy of the consumer/manufacturer/country
- Quality cannot be assessed by merely testing the product
- Quality should be built into a Product
- NSQ - harm the health, affect reputation of the company, business
- GMP is a Mandatory Standard to ensure Quality

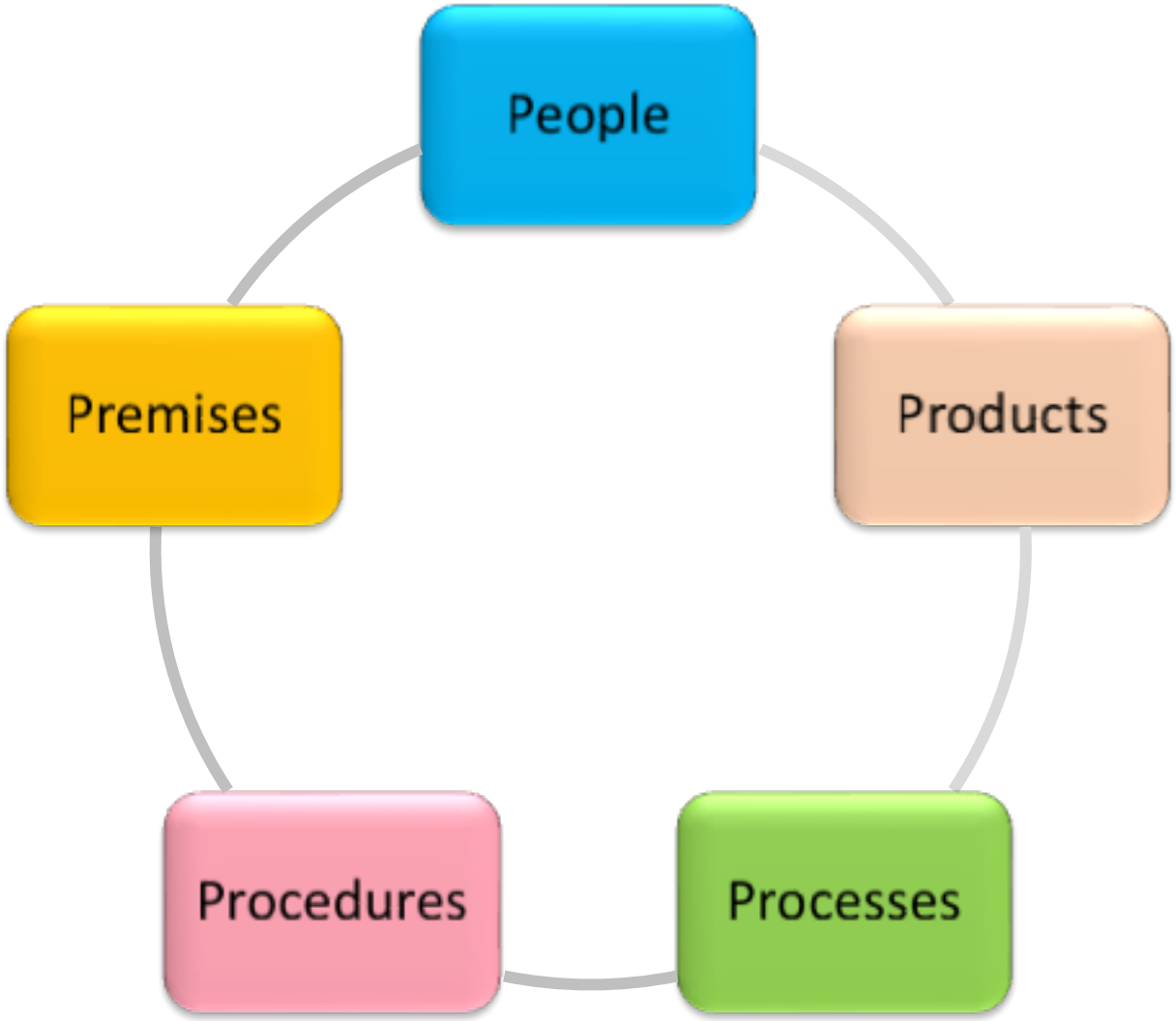
Why GMP?

- To avoid mix-ups
- To avoid contamination
- To avoid cross-contamination
- To produce consistent quality
- To assure quality till end of shelf life
- To avoid any errors
- To ensure quality of drugs and Patient safety
- To build trust and confidence

Why do need revision of Schedule M

- GMP is dynamic
- Substantial Improvement in concept of quality
- Convergence (Harmonization) with global standards
- Technological developments
- New Formulations/Therapies
- Quality Awareness
- Quality culture
- Pharmacy of the world (Opportunities in the global market)

Principles of GMP



Components of GMP(existing)

- General requirements
- Ware housing area
- Production area
- Ancillary areas
- Quality control area
- Personnel
- Health, clothing, sanitation of workers
- Manufacturing operation and controls
- Sanitation in manufacturing premises
- Raw materials
- Equipment
- Documentation and records
- Labels and other printed material

- Quality assurance
- Self inspection and quality audits
- Quality control system
- Specifications
- Master formula records
- Packaging records
- Batch packaging records
- Batch processing records
- SOP’s and records
- Reference samples
- Reprocessing and recoveries
- Distribution records
- Validation and process validation
- Product recalls
- Complaints and adverse reactions
- Site master file

Critical Components of GMP

Ventilation System - HVAC

To provide

- Filtered air of adequate quantity and cleanliness
- Environmental control so that the product remains under the required conditions.
- Adequate temperature and relative humidity for product protection.
- Personnel comfort

What is achieved:

- To avoid contamination
- To ensure quality

Pharmaceutical Water

Low Quality Water:

- Product degradation
- Product contamination
- Seasonal and regional variation

Types of water contaminant

- Particles or Suspended Solids
- Dissolved Solids (Ionized & Non-ionized)
- Colloidal Materials
- Dissolved Gases
- Bacteria and other living organisms

Stability Studies

To provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as

- Temperature
- Humidity
- Light

- Stability testing permits the establishment of the Storage conditions, Retest periods / Shelf life, and Recommended Packaging.

- Meet Regulatory Requirements / Product Registration.

Comparison Between Existing Schedule M And Draft Upgraded Schedule M

PART-I : Good Manufacturing Practices for Pharmaceutical Products: Main Principles

1. Pharmaceutical Quality System

- Manufacturer must assume the responsibility for the quality.
- Senior management has the ultimate responsibility.
- Consistency in the quality
- Product and process knowledge
- Materials from approved vendors
- Production and release as per conditions of license and other applicable regulations

1. Pharmaceutical Quality System

- Approval of planned changes
- Notification of changes to the regulators
- Continual improvement in the quality
- Regular review of quality
- Root cause analysis of defective products
- Periodic management review
- Quality Manual

2. Quality Risk management

- **QRM:**
  - Assessment of risk, Control of risk, Communication of risk, Review of risk
- **Product quality review**
  - starting materials, critical in-process control and finished products results.
  - review of all batches that had failed.
  - Review of non-conformance related investigation and corrective and preventive action taken.
  - Review of complaints and recalls etc.
  - Qualification status of equipments such as heating, ventilation and air-conditioning, water and compressed gases.
  - Even for exported products
  - Annually
  - Technical agreements, up-to-date.

3. Good Manufacturing Practices

Definition: Part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the licence

Aim:

Managing and Minimizing Risk

4. Sanitation

Existing :

Covers only Workers and manufacturing premises

New:

Covers personnel, premises, equipment/ apparatus, production materials and containers.

5. Qualification and Validation

Validation:

Existing:

Covers only manufacturing process, testing and cleaning

New:

Also covers Premises, Utilities and equipment

Qualification:

Existing: No provision

New:

Premises, Utilities, equipment, process (DQ, IQ, OQ, PQ)

6.Compliance and Adverse reactions

Existing:

- Serious Adverse drug reactions reported to Licensing Authority

New:

- Faulty manufacture, product deterioration, serious quality problems reported to Licensing authority
- Pharmacovigilance system should be in place

7. Product Recall

Existing:

- No provision to inform to LA

New:

- To be informed to LA
- Comprehensive system specified for promptly and effective recall

8.Change Control

Existing:

- only in case of significant changes

New:

- Changes in RM, PM, Specifications, Analytical methods, Facilities, Utilities, Equipment, processing steps, labeling Software etc
- Minor, Major and Critical Changes based on nature and extent

9.Production

Existing:

No details of Contract giver, contract acceptor, Contract analysis

New:

- Role and Responsibilities of Contract giver, Contract Acceptor
- Agreement
- Technology Transfer

10.Self Inspection, Quality Audits and Supplier Audit and approval

Existing:

- Frequency-performed routinely and in specific occasions ie recall or inspection by LA

New:

- At least once in a year
- Suppliers audit and approval (approved list of RM and PM)

11.Personnel

New:

- Organization chart
- Personnel should be motivated to support maintenance of high quality standards
- Role and responsibilities of Key personnel(heads of production, QC)
- Qualification of key personnel (as specified under Rules)
- Functions may be delegated, but not responsibilities
- Visitors entry procedures into production area
- Approved training program

12.Premises

Detailed requirements about premises including

- production areas,
- **weighing areas,**
- ancillary areas,
- storage area,
- production areas,
- quality areas,
- equipments,
- materials,
- reference standards etc. have been prescribed.

13. Equipment

- Validated Cleaning procedures

14.Materials

New:

- Validated Computerized storage systems
- PM – not to test all batches, but based on vendor approval and statistical data analysis
- Identity test for each container of Starting material (Exception- dedicated facilities)
- Reworking of rejected products (new batch number)
- Part of earlier batches into a batch of the same product at defined stages of manufacture
- Extension of retesting date (Para 10.9 of Schedule M)

15.Reference Standard

New:

- IP RS/IS procured from IPC
- Procedure for working standard

16.Waste Materials

- By and large similar provisions

17. Documentation

Exist:

- MFR, SOP in hard copy for verification

New:

- Audit trail- to ensure existence of documented evidence, traceability
- MFR – Hold time permitted for Intermediates and in-process materials
- Validation Master Plan

18. Good Practices in Production

- Detailed requirements about Good practices in production have been provided.
- Deviation control
- Prevention of cross contamination, measures to be taken
- Timeline for storage of equipment after cleaning
- Any significant deviation from the expected yield shall be recorded and investigated
- Line clearance for packaging operations

19. Good Practices in Quality Control

- Detailed requirements about Good practices in QC have been provided.
- The detailed requirements of stability studies of finished products and, when necessary of starting materials and intermediate products, establishing shelf life including written programme for ongoing stability determination have been specified.
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- Stability shall be determined prior to marketing and following any significant changes e.g. changes in in-process, equipments or packaging materials.
- Part testing, incase CoA from the reliable manufacturer
- Retention sample of other materials – Minimum of two years
- Retest date

20. Computerised Systems

- Detailed requirements about validation of GMP related computerized system have been prescribed.
- IQ and OQ of Hardware and Software
- Proper backup system

Applicability of WHO Guidelines

The guidelines published by WHO on following aspects relating to GMP through their Technical Report Series from time to time may be considered for general guidance purposes:-

i. Guidelines on the principles of airflow directions, air filtration standards, temperature, humidity and related parameters.

ii. Good manufacturing Practices (GMP) guidelines regarding the design, installation and operation of pharmaceutical water systems including guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms.

iii. Guidelines on design, installation, qualification and maintenance of the Heating, Ventilation, Air Conditioning (HVAC) systems of the manufacturing plant.

iv. GMP guidelines for validation.

v. Guidelines on packaging of pharmaceutical products

PART-II :Specific Requirements for Manufacture of Sterile Products, Parenteral Preparations (Small Volume Injectables & Large Volume Parenterals) and Sterile Ophthalmic Preparations

Existing Schedule M	Draft rules (Upgraded Schedule M)
Requirements have been provided in Schedule M but with out reference to the latest requirements/updates.	Separate comprehensive provisions on Specific Requirements for Manufacture of Sterile Products, Parenteral Preparations (Small Volume Injectables and Large Volume Parenterals) and Sterile Ophthalmic Preparations in line with WHO-TRS have been prescribed.

PART-III :Specific Requirements for Manufacturing of Pharmaceutical Products Containing Hazardous Substances Such as Sex Hormones, Steroids (Anabolic, Androgenic) or Cytotoxic Substances

Existing Schedule M	Draft rules (Upgraded Schedule M)
No such separate provision about requirements for manufacturing of pharmaceutical products containing these substances. However there are provisions that processing of these sensitive drugs must be done in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differentials.	Separate comprehensive provisions on Specific Requirements for Manufacturing of Pharmaceutical Products Containing Hazardous Substances Such as Sex Hormones, Steroids (Anabolic, Androgenic) or Cytotoxic Substances.

PART-IV: Specific Requirements for Manufacture of Biological Products

Existing Schedule M	Draft rules (Upgraded Schedule M)
No such separate provisions for comprehensive provisions on specific requirements for manufacture of biological products have been prescribed.	Separate comprehensive provisions on Specific Requirements for Manufacture of Biological Products

PART-V : Specific Requirements for Radiopharmaceutical Products

Existing Schedule M	Draft rules (Upgraded Schedule M)
No such separate provisions for specific requirements for radiopharmaceutical products have been prescribed	Separate comprehensive provisions on Specific Requirements for Radiopharmaceutical Products

PART-VI: Specific Requirements for Phytopharmaceuticals

Draft rules (Upgraded Schedule M)	Existing Schedule M
Separate comprehensive provisions on Specific Requirements for Phytopharmaceuticals.	No such separate provisions for specific requirements for phytopharmaceuticals have been prescribed.

PART-VII: Specific Requirements for the Manufacture of Investigational Pharmaceutical Products for Clinical Trials in Humans

Draft rules (Upgraded Schedule M)	Existing Schedule M
Separate comprehensive provisions on Specific Requirements for the manufacture of Investigational Pharmaceutical Products for Clinical Trials in Humans	No such provisions on specific requirements for the manufacture of investigational pharmaceutical products for clinical trials in humans have been prescribed.

The parts related to

- Oral solids,
- Oral liquids,
- Topical preparations,
- Active pharmaceutical ingredients and
- Meter-dose inhalers

are similar in the proposed rules as present in the existing Schedule M of the Drugs and Cosmetics Rules, 1945.

Conclusion

- GMP is Dynamic
- Continual improvement in the quality
- Facilitate Innovation
- Promote exports
- On par with Global Standards
- Built trust and confidence on quality
- Reduce NSQ and product failures
- Reduce Recall


Thank you