Revised Godd Manufacturing Practice (GMP) requirements for Active Pharamceutical Ingredients (API)

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Outline

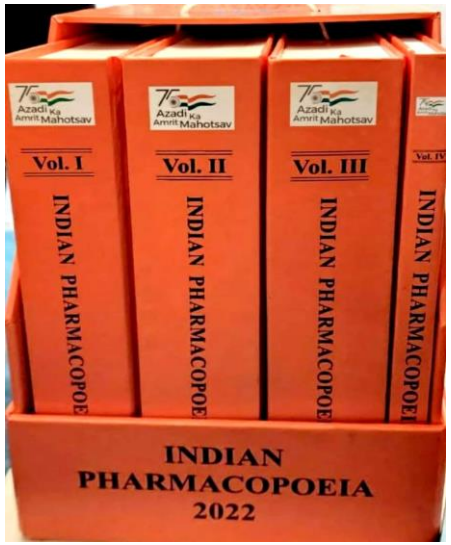
- Pharmaceutical Regulation and its framework
- Standards and Indian Pharmocopiea
- API Approval and post licensure Control
- Salient features of revised GMP code for API

Pharmaceutical regulation and its framework

- **Pharmaceutical Regulation in India**
  - Ensuring **Safety, Efficacy** and **Quality** of Drugs
- **Regulatory Bodies**
  - Central Drugs Standard Control Organization (CDSCO) headed by Drug Controller General of India (DCGI)
  - State Drug Control Authorities

CENTRAL DRUGS STANDARD CONTROL ORGANISATION
CDSCO CDSCO
सत्यमेव जयते
MINISTRY OF HEALTH - GOVERNMENT OF INDIA

State Drug Control Authority



Pharmaceutical regulation and its framework

Definition of Drug (Drugs and Cosmetic Act Section 3 (b):

- All **medicines** for internal or external use of human beings or animals and all **substances** intended to be used for or in the **diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals.**
- **Substances** other than food products which alters the structure of human body or helps in the destruction of insects or vermin that cause the diseases.
- **Substances intended to be used as components of drug** including empty gelatine capsule etc.
- **Devices** which are intended for the purpose of internal or external use in diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals.

Standard of Quality: Section 8 & 16 read with Second Schedule: (a) in relation to a drug, that the drug complies with the standard set out in 6[the Second Schedule]

Second Schedule : Standards to be complied with by i**mported drugs and by drugs manufactured** for sale, sold, stocked or exhibited for sale or distributed :

5 (a) Standards of **identity, purity and strength** specified in the edition of the **Indian Pharmacopoeia** for the time being in force and such other standards as may be prescribed.

(b) **Drugs not included in the Indian Pharmacopoeia** but **which are included in the official Pharmacopoeia of any other country.**

Indian Pharmocopoeia (IP)

- Indian Phamocopia Commission (IPC) - Setting Standards for Drug Quality by publishing standard of Drug Quality
- Role of IPC in Drug Regulation:
  - Ensuring drug quality and safety
  - Setting standards for test / analysis
  - Providing reference materials (IPRS, Impurities etc)
  - Supporting drug approval and licensing processes wherever required.
- Monographs includes Chemical structure, description, solubility, identification tests, assays, and impurities

Approval Process

- **Steps of drug approval (New Drug-API and formulation)**
  - License for manufacture of new API for test / analysis
  - Preclinical studies / Clinical trials (Phase I-IV)
  - New Drug Application (NDA) submission - Formulation & API
  - Review and approval by CDSCO

- **Steps for drug approval (not a New Drug)**
  - Stability studeis under Test License (Form 29)
  - Application for manufacring of API
  - Joint inspection
  - Review and approval by State Licensing Authority (SLA)

Post Marketting / Licensure Control

- Adverse drug reporting
- Pharmacovigilance programme of India
- Good Manufactuirng and product Inspections
  - Revalidation of licence and GMP Certification
  - GMP Code revised vide GSR 922 (E) dated 28.12.2023
- Sampling of drugs for the purpose of test / analysis

Revised Schdule M (GSR 922)-salient features

- **Pharmaceutical Quality System (PQS):** Implementing a quality system to ensure the quality of pharmaceutical products.
- **Quality Risk Management (QRM):** Conducting risk assessments and implementing measures to mitigate risks. (eg. Nitrosamine impurities)
- **Product Quality Review (PQR):** Regularly reviewing the quality of products to ensure compliance with regulations.
- **Qualification and Validation:** Validating equipment and processes to ensure they meet quality standards.
- **New addtions:** Guidelines for pharmaceutical products containing hazardous substances, such as sex hormones, steroids, cytotoxic substances, biological products, and radiopharmaceuticals.
- **Implementation timelines:** Medium and small manufacturers have 12 months, while large manufacturers have six months, to implement the revised rules from 28.12.2023 .
- **Part XII Specific requirement for manufacture of API**

Introduction to Part XII

- Main prinicples as stipulated in Part I mandatorily applies
- Applies to APIs for use in Finished Pharmaceutical Products (FPP)
- Sterile API - GMP guidelines of sterile products applies
- Covers APIs manufactured by chemical sysnthesis, cell cuture or fermentaion by recovery from natural sources or by any combination of these processes.
- Defines API starting material - "a significant structural fragment of API with defined chmeical properties to which this guidance applies".

Part XII Specific requirement for manufacture of API

Type of manufacturing	Application of this guide to steps (shown in green) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API Starting material into process	Production of intermediates	Isolation and purification	Physical processing and packaging
API derived from animal Source	Collection of organ, fluid or tissue	Cutting, mixing or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
Phytopharmaceutical extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants or cultivation and harvesting	Cutting or comminuting			Physical processing and packaging
Biotechnology: fermentation or cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

Various components of Part XII of GMP code

- **Quality Management**
  - Quality Unit and its responsiblity
  - Intgernal Audits (Self inspections), Porduct Quality Review (PQS)
- **Personnel**-Qualification, hygiene, consultants
- **Building and facility**
  - Design & construction, Utilites, Lighting, sanitation & maintenance
  - Water, sewage and refuse
  - Containment-cytotoxic, penicillines, etc.
- **Process equipment**
  - Design & constructioin, maintenance & cleaning, Caliberation
  - Computerised system
- **Documentation and Records**
  - System and specifications, Cleaning records
  - Records of RM, Intermediate, labelling etc.
  - MPR / BPR, Laboratory Control Records, Review records
- **Material Management**
  - Receipt, Quarantine, sampling,
- **Production and in-process controls**
  - Operation, Time limits, In-process sampling
  - Bledning baches, Contamination Control
- **Pacakging and identification labelling of APIs and intermediates** - operation and controls
- **Storage and distribution**
  - Warehousing and Distribution procedures
- **Laboratory Controls**
  - Tesing of intermediates /API, CoA,
  - Stability Monitoring, Expirty & retest dating
  - Reserve / Control samples

Various components of Part XII of GMP code

- **Validation**
  - Policy, Documentation, Qualification, Approches to PV,
  - PVP, Periodic review system,
  - Cleaning Validation, Analytical method Validation,
- **Change control**
- **Rejection and reuse of materials**
  - Rejection, Reprocessing, Reworking
  - Recovery of materials and solvents
  - Retuns
- **Complaints and recalls**
- **Contract manufactures (including laboratoreis)**
- **Specific guidance for APIs manufactured by cell culture or fermentation**
  - Cell Bank Maintenance and record keeping
  - Cell culture or fermentation
  - Harvesting, isolation and purificatioin
  - Viral removal or inactivation steps
- **APIs for use in clinical trials**
  - All controls not applicable / clinical material, Quality measures
  - Equipment and facilities
  - Production, Validation, Change and Lab Controls
  - Documentation

Thank you
for your attention