Recent advancements in Indian Regulations with reference to Draft Amendment of Schedule M

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Outline

- Introduction (about CDSCO and various other regulatory authorities in the country)
- Background Information on GMP
- Content of Schedule-M, 2001
- Content of GSR-999(E) dated:05-10-2018 Draft Schedule-M
- Salient features of Draft Schedule M
- Some recent initiatives

VISION

To protect and promote public health in India

CDSCO

MISSION

To safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices.

CDSCO

CDSCO – GEOGRAPHICAL LOCATION

CDSCO ZONES

- North Zone (Ghaziabad)
- West Zone (Mumbai)
- South Zone (Chennai)
- East Zone (Kolkata)
- Zone (Ahmedabad)
- Zone (Hyderabad)

CDSCO SUB ZONES

- Sub Zone (Bengaluru)
- Sub Zone (Baddi)
- Sub Zone (Jammu) and (Goa)

Port Offices/Airports : 13
Laboratories : 7

- New Sub/Z Offi : Varanasi, Vizag, Guwahati, Indore

CDSCO Offices

Zonal Offices:

- Ghaziabad, Mumbai, Chennai, Kolkata, Ahmedabad and Hyderabad

Sub Zonal Offices:

- Baddi, Bengaluru, Goa, Jammu, Varanasi, Guwahati, Indore.

Port Offices: (13)

Central Drugs Laboratories – 7

- Kolkata, Mumbai, Chennai, Hyderabad, Chandigarh, Guwahati and Kasauli

CDSCO

- At present CDSCO is functioning at FDA Bhawan, Kotla Road since 2008.

CDSCO has six zonal offices, seven sub-zonal offices, 13 port offices and seven laboratories under its control. CDSCO is assisted by Central and Regional Drug Laboratories. In addition, each Indian State has its own State regulatory body.

Historical Background

- **Schedule-M first published vide GSR 735 (E), 24th June, 1988**
- **Revised Schedule M vide GSR 894 (E) , 11th December, 2001 in accordance with international GMP guidelines**
- **Applicable to all the drug manufacturing units in India w. e. f. 1-7-2005.**
- **Draft Schedule M published vide GSR 999(E) dated 05.10.2018**

Background Information

- The first WHO draft text on GMP was adopted in 1968. In 1969, when the World Health Assembly recommended the first version of the WHO Certification Scheme on the quality of pharmaceutical products moving in the global market, it accepted the WHO GMP as an integral part of the Scheme.

- A supplementary annex on biological medicinal products was adopted by the Expert Committee on Biological Standardization (ECBS) in 1991 and establishes the general approach to the quality control of biological medicines that include products such as vaccines, blood and blood products, antigens, cell and tissue therapies, biopharmaceutical products, and others.

- More than 100 countries have incorporated the WHO GMP provisions into their national medicines laws, and many more countries have adopted its provisions and approach in defining their own national GMP requirements.

- The WHO GMP continues to be used as a basis for the WHO Certification Scheme and prequalification of vaccines for procurement by UN agencies.

What is GMP?

- Good manufacturing practices is that 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 license, clinical trial permission or product specification.
- Good manufacturing practices are concerned with both production and quality control.
- Good manufacturing practices are aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

Existing Schedule M-2001

- **Part-1** Good Manufacturing Practices for Premises and Materials
- **Part -2** Requirement of Plant and Equipment
- **Part-1A:** Requirement for manufacture of Parenterals and Ophthalmic
- **Part -1B:** Requirement for Manufacture of oral Solid Dosage (Tablets and Capsule)
- **Part 1C:** Specific Requirement for manufacture of Oral Liquids
- **Part 1D :** Specific Requirement for manufacture of External Preparations
- **Part 1E:** Specific Requirement for manufacture of Metered Dose Inhalers (MDI)
- **Part 1F :** Specific Requirements of Premises, Plant and materials for manufacture of Active Pharmaceutical ingredients (Bulk Drugs)

Draft Schedule M-2018

- Part-I Good Manufacturing Practices for Pharmaceutical Products _ **Main Principles**
- Part -II Specific Requirement for manufacture of **Sterile Products , Parenteral Preparations(SVP & LVP), and Sterile Ophthalmic Preparations**
- Part-III: **Specific Requirement for manufacture of products containing hazardous substances such as Steroids (Anabolic and Androgenic), Sex Hormones and Cytotoxic Products**
- Part IV: Specific Requirement for manufacture of **Biological Products**
- Part V : Specific Requirement for manufacture of **Radio Pharmaceuticals**
- Part VI : Specific Requirement for manufacture of **Phyto Pharmaceuticals**

Draft Schedule M- 2018

- Part-VII: Specific Requirements for manufacture of **Investigational Pharmaceutical Products for Clinical Trials in Humans**
- Part –VIII: Specific Requirements for manufacture of **Oral Solid Dosage forms (Tablets and Capsules)**
- Part -IX : Requirement for manufacture **of Oral Liquids (Syrups, Elixir, Emulsions and Suspensions)**
- Part- X: Specific Requirements for manufacture of **External Preparation (Ointments, Creams, Emulsions, Solutions , Lotions, Dusting powders and identical Products)**
- Part XI : Specific Requirements for manufacture of **Metered Dose- Inhalers (MDI)**
- Part XII: Specific Requirements for manufacture of **Active Pharmaceutical Ingredients (API)**
- Part XIII: Requirements of Plant and Equipment.

Draft Schedule M- 2018

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

1. **Pharmaceutical Quality System**
2. **Quality Risk Management**
3. **Good Manufacturing Practices for Pharmaceutical Products**
4. **Sanitation and Hygiene**
5. **Qualification and Validation**
6. **Complaints**
7. **Product Recall**
8. **Change Control**
9. **Product under Loan License or Contract and Contract Analysis and other activities**
10. **Self Inspection, Quality Audit ,Vendor/supplier's audit and approval**
11. **Personnel**

Draft Schedule M-2018

12. Training
13. Personal Hygiene
14. Premises
15. Equipment
16. Materials
17. Reference Standards
18. Waste Materials
19. Documentation
20. Good Practices in Production
21. Good Practices in Quality Control
22. Computerized System

Appendix I– Site Master File

Some Salient features

- Pharmaceutical Quality Systems (PQS) is incorporated which is not present in the current Schedule M.
- Quality Risk Management (QRM) is incorporated to evaluate the risk to quality based on scientific knowledge with the process and ultimately links to the protection of the patient.
- Change control is incorporated in the revised Schedule M to evaluate all changes that may affect the production and quality of the product.
- Suppliers audit and approval is incorporated.
- Stability studies requirements have been elaborated in the revised Schedule M

Pharmaceutical Quality system

- Manufacturer should assume responsibility for Quality of Pharmaceutical products, so that the product is fit for intended use.
- Senior Management must be engaged and responsible to institutionalize Quality system Principles with commitment of staff at all levels right from manufacturing till the product is distributed.
- Quality System should be designed to incorporate current Good Manufacturing Practices and Quality Risk Management comprehensively.
- Pharmaceutical Quality system- applies to the life cycle stages i.e. from manufacturing of IMP (Investigational Medicinal product), Technology transfer to Commercial production till the discontinuation of a product).
- The product quality system can extend to the pharmaceutical development life-cycle stage and shall facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities

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Pharmaceutical Quality system

- Continual Improvement in Process and Product Quality with knowledge of process and product Quality trend.

- There should be Quality Risk Management established in organization to identify the risk factors at all levels , and at each life cycle stages , and to mitigate the risks by implementing CAPA for Quality improvement.

- Deviations (identified in Quality system , Process, operations, Quality controls) are timely detected , logged , investigated to find out right root cause /most likely root cause , CAPA identified , implemented and CAPA effectiveness monitored.

- Periodic Management Review : Regular Participations of Senior Leadership in review of causes of escalation such as -non-conformances, deviation , complaint trends , Product Quality defects , Quality System trends to identify opportunity for continual Improvement Actions and resolution to Process issues and improvement in Product Quality System.

Product Quality Review

- Regular, periodic or rolling quality reviews of all medicinal products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements.
- The manufacturer shall evaluate the results of the review and an assessment shall be made as to whether corrective and preventive actions or any revalidation shall be undertaken, under the product quality system.
- Corrective and preventive actions shall be completed in a timely and effective manner, according to documented procedures.
- There shall be procedures for the on-going management and review of these actions, and the effectiveness of these procedures shall be verified during self-inspection.
- Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. There shall be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review.
- The authorized person responsible for final batch certification shall ensure that the quality review is performed in a timely manner and is accurate.

Change Control

- A formal change control system shall be established to evaluate all changes that may affect the production and control of the product.
- Written procedures shall cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.
- Any proposals for relevant changes to GMP shall be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).
- The potential impact of the proposed change on the quality of the intermediate or API or finished product shall be evaluated.
- When implementing approved changes, measures shall be taken to ensure that all documents affected by the changes are revised.
- After the change has been implemented there shall be an evaluation of the first batches produced or tested under the change.
- The potential for critical changes to affect established retest or expiry dates shall be evaluated. If necessary, samples of the intermediate or API or finished product produced by the modified process can be placed on an accelerated stability programme and/or can be added to the stability monitoring programme.

Production under loan license or contract and contract analysis and other activities

Principle:

Production under loan license or contract and contract analysis and any other activity covered by good manufacturing practices must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

Loan licensee or contract giver:

The product quality system of the loan licensee or contract giver shall include the control and review of any outsourced activities. The contract giver is responsible for assessing the legality, suitability and competence of the manufacturing facility provider or contract acceptor to successfully carry out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of good manufacturing practices incorporating quality risk management principles are followed.

Manufacturing facility provider or contract acceptor :

The manufacturing facility provider or contract acceptor must have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the loan licensee or contract giver. Contract manufacture shall be undertaken only by a manufacturer who holds a valid manufacturing license.

Good Practices in Quality Control

- **Stability studies:** QC should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.
- QC should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
- A written program for on-going stability determination should be developed and implemented to include elements such as: (a) a complete description of the medicine involved in the study; (b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability; (c) provision for the inclusion of a sufficient number of batches; (d) the testing schedule for each medicine; (e) provision for special storage conditions; (f) provision for adequate sample retention; (g) a summary of all the data generated, including the evaluation and the conclusions of the study.
- Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials etc.

Computerized Systems

- GMP-related computerized systems shall be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.
- Appropriate installation qualification and operational qualification shall demonstrate the suitability of computer hardware and software to perform assigned tasks.
- Computerized systems shall have sufficient controls to prevent unauthorized access or changes to data. There shall be controls to prevent omissions in data (e.g. the system being turned off and data not captured). Written procedures shall be available for the operation and maintenance of computerized systems.
- Where critical data are being entered manually, there shall be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.
- A back-up system shall be provided so that there is no permanent loss of records due to system breakdown or failure. Means of ensuring data protection shall be established for all computerized systems.

CDSCO Initiatives

Initiatives

e-Governance:

- CDSCO launched SUGAM which was developed in phases. In the latest phase the following processes for drugs and Cosmetics have been digitized and now the applications have to be filed through online only.
- Applications for grant of Permissions for marketing of New Drug, Fixed Dose Combination New Drug, Subsequent New Drug, Vaccines, Recombinant Based Drugs etc.
- A module for creation of database for all the manufacturing facilities in the country and the products approved for marketing has been developed and launched under SUGAM portal aimed to provide a comprehensive data base of all the manufacturing facilities approved in the country along with the products permitted to be marketed by them.
- Mandated under GSR 19 (E) , dated 10.01.2019 with insertion of Rule 84AB
- CDSCO has developed a new website www.cdsco.gov.in with latest features and complying GIGW guidelines issued by the Government of India. The website provides easy browsing, search facility, improved user experience etc.
- CDSCO has seven Laboratories under it which are engaged in test/analysis of Drugs, Cosmetics, Medical Devices and Vaccines. A portal digitizing various functionalities of the laboratories has been developed which is known as SUGAMLABS. A portal will enable timely testing of drugs, maintain integrity and traceability of samples.
- CDSCO has launched a portal www.cdscomdonline.gov.in exclusively for filing of applications their processing and tracking, both for Central and State Governments. This portal is a single window platform for obtaining manufacturing and import licenses, clinical investigations, marketing of new medical devices etc. This has further enhanced ease of doing business, enabled transparency, accountability and predictability.

Recent Advancements in Indian Regulations:

Clinical Trials:

- Realizing the importance of clinical trial in development of new drugs to cope up with the challenges of disease burden in public health care, the CDSCO and the Ministry of Health and Family Welfare have taken various measures to promote the scientific and ethical clinical trials in the country.
- New Drug and Clinical Trial Rules, 2019 have been published vide G.S.R 227 (E) dated 19/03/2019, which contains various provisions for improving transparency, accountability and also research and development of new drugs.

Medical Devices:

- For regulation of manufacture, import, clinical investigation, sale of medical devices, new Medical Device Rules, 2017 have been published on 31.01.2017 & effective from 01.01.2018.The Rules contain various provisions for improving transparency, accountability and promote research and development of new devices .

Recent Advancements in Indian Regulations

Ease of Doing Business

- **Increasing the Validity WHO COPP:** CDSCO has issued Office Memorandum to extend the validity of certificate of Pharmaceutical product (COPP) under the WHO GMP Certification Scheme from 2 years to 3 years subject to condition that the GMP status of the manufacturing facility should be monitored as per WHO guidelines through inspection on a periodic interval.
- **Waiver of NOC for export purpose:** CDSCO has issued a notice to remove the requirement of No Objection Certificate (NOC) with respect to shipping bills from the port offices of the CDSCO for the export consignments to any country if such shipping bills are filed by the manufacturer himself, having valid licence under Drugs and Cosmetics Act.
- **Delegation of power to the States:** CDSCO has delegated power to all state/UTs drug controllers for issuance of No Objection Certificate (NOC) with respect to unapproved / Banned drugs for export purpose only.

Initiatives

Good Clinical Practices(GCP) guidelines

CDSCO constituted expert committee to examine the CDSCO GCP guidelines vis-à-vis GCP guidelines of ICH, WHO & other agencies to give its recommendation to align Good Clinical Practices(GCP) guidelines for clinical trials in India with Global Good Clinical Practices(GCP) guidelines for standards , roles and responsibilities of sponsors, investigators, ethics committee, etc.

Regulation of Cosmetics and Blood banks

CDSCO has proposed a separate set of comprehensive Rules for Cosmetics and Blood Banks.

Salient Features

- Risk based classification
- Provisions of Notified Bodies
- Quality Management System in line with ISO 13485 has been adopted;
- Provisions related to the ‘Essentials Principles of Safety and Performance’ for manufacturers have been specified in the Rules;
- Separate provisions for regulation of Clinical Investigation of investigational medical devices (i.e. new devices) have been made at par with international practice.
- Provision is made to designate or establish Central Government medical device testing laboratories to verify conformance with the quality standards.

S No.	Name of the device	Notification Number	Date of notification
1	Disposable Hypodermic Syringes	GSR 365 (E)	17-03-1989
2	Disposable Hypodermic Needles	GSR 365 (E)	17-03-1989
3	Disposable Perfusion Sets	GSR 365 (E)	17-03-1989
4	In vitro Diagnostic Devices for HIV, HbsAg, HCV	GSR 601(E)	27-08-2002
5	Cardiac Stents	S.O. 1468 (E)	06-10-2005
6	Drug Eluting Stents	S.O. 1468 (E)	06-10-2005
7	Catheters	S.O. 1468 (E)	06-10-2005
8	Intra Ocular Lenses	S.O. 1468 (E)	06-10-2005
9	I.V. Cannulae	S.O. 1468 (E)	06-10-2005
10	Bone Cements	S.O. 1468 (E)	06-10-2005
11	Heart Valves	S.O. 1468 (E)	06-10-2005
12	Scalp Vein Set	S.O. 1468 (E)	06-10-2005
13	Orthopedic Implants	S.O. 1468 (E)	06-10-2005
14	Internal Prosthetic Replacements	S.O. 1468 (E)	06-10-2005
15	Ablation Devices	S.O.237(E)	25.01.2016

Cont..

The Products which were already regulated as ‘drugs’ but now fall under the scope of Medical Devices Rules, 2017:-

16. Blood Grouping Sera
17. Ligatures, Sutures and Staplers
18. Intra Uterine Devices (Cu-T)
19. Condoms
20. Tubal Rings
21. Surgical Dressings
22. Umbilical tapes
23. Blood/Blood Component Bags
24. Disinfectant

Newly notified medical device

S No.	Name of the device	Effective from	Notification Number	Date of notification
25	Nebulizer	01.01.2021	S.O. 5980(E)/4671 (E)	03.12.2018/27.12.2019
26	Blood Pressure Monitoring Device	01.01.2021	S.O. 5980(E)/4671 (E)	03.12.2018/27.12.2019
27	Glucometer	01.01.2021	S.O. 5980(E)/4671 (E)	03.12.2018/27.12.2019
28	Digital Thermometer	01.01.2021	S.O. 5980(E)/4671 (E)	03.12.2018/27.12.2019
29	Organ Preservative Solution	02.04.2019	S.O. 1500(E)	02.04.2019
30	All implantable medical devices Equipment	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
31	CT Scan Equipment	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
32	MRI Equipment	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
33	Defibrillators	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
34	PET Equipment	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
35	X-Ray Machine	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
36	Dialysis Machine	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
37	Bone marrow cell separator	01.04.2021	S.O. 775 (E)/4672 (E)	08.02.2019/27.12.2019
38	Ultrasound	01.11.2020	S.O. 3721 (E)	16.10.2019

Salient features-NDCT

- Effective from 19.03.2019
- New Drugs definition scope has been broadened to include
  - Phytopharmaceuticals
    - living modified organism,
    - monoclonal anti-body,
    - stem cell derived product,
    - gene therapeutic product or
    - xenografts
- Waiver to Academic Clinical Trials
- Provision for Pre and Post-submission meeting

Salient features-NDCT

- Provisions of Accelerated Approval to a new drug for a disease or condition, taking into account
  - Severity, rarity, or prevalence and
  - the availability or lack of alternative treatments
  - provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment.
- Provisions for pre-consultation have been incorporated
- Orphan drugs intended to treat a condition which affects not more than five lakh persons in India
- Separate Provisions for Registration of Ethics Committee for
  - BA/BE study
  - Marketing Authorization

Salient features-NDCT

- Reduction in time lines for approval

Type of Application	Timelines
CT (innovated in India):	within 30 working days
CT (if drug is already approved by other country):	within 90 working days
New drug	within 90 working days
Processing of Import License	90 working days
If the central licensing authority fails to communicate, the “permission to conduct the clinical trial shall be deemed to have been granted”.	

Draft Cosmetics Rules

- Draft rules for cosmetics published vide GSR 1153 dated 29.11.2018
- Comprise of 9 Chapters and 13 Schedules
- The concept of establishment and function of **Central Cosmetic Laboratory** introduced.
- Duration of the Import RC is extended from 3 years to 5 years.
- Any person can import already registered cosmetic without any further registration just by giving an undertaking under prescribed format at the port of entry.

Draft Cosmetics Rules

- **Inspection of foreign manufacturing site** by the inspector is introduced for which expense is to bear by RC holder

- Verification for the compliance of manufacturing licence is to be done **once in two years**.

- **Manufacturing Licence shall remain valid in perpetuity**, subject to payment of licence or loan licence **retention fee** at the end of validity of licence

- Separate chapter for procedure of sampling for test or analysis, seizure and report has been introduced.

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Thank you