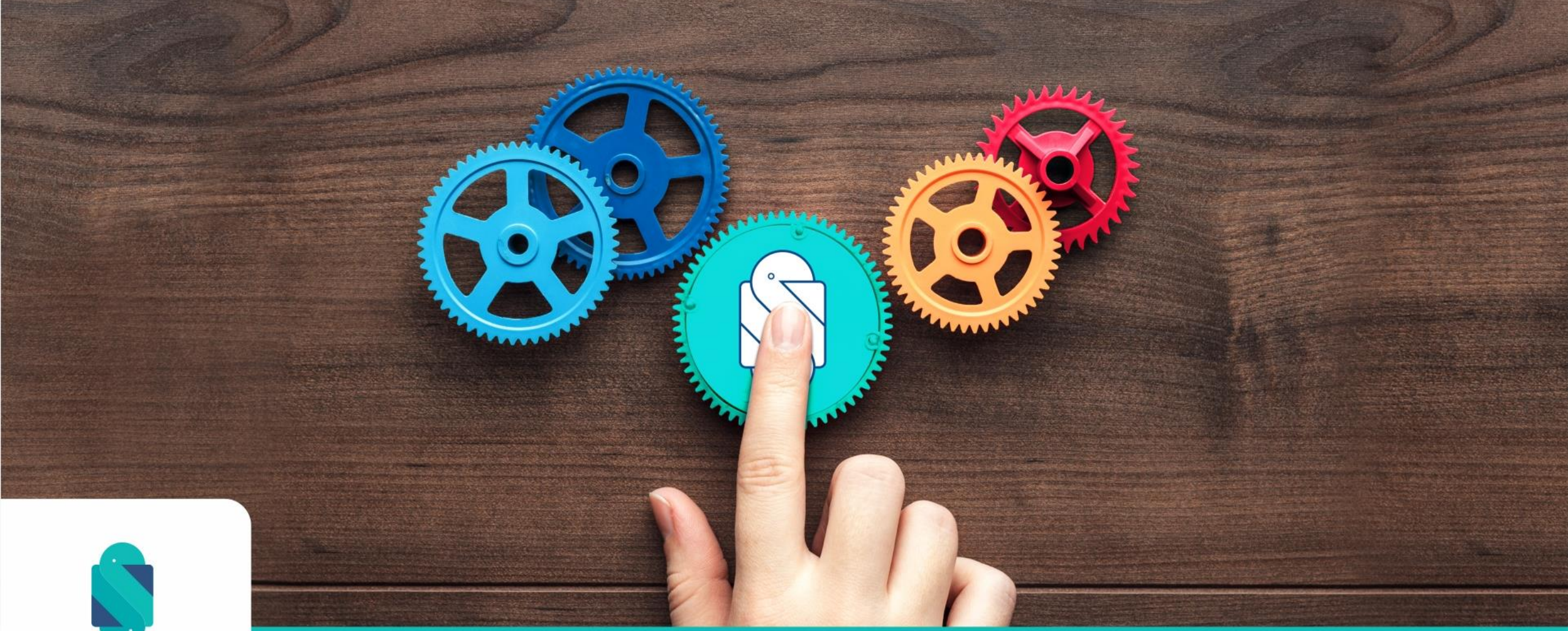

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Overview of Revised Schedule M

Oct 2024

Agenda

- Background to revised Schedule M
- Impact of non-compliance against revised Schedule M
- Indian suppliers: Incidence due to non-compliance of Good Manufacturing practices
- Evolution of schedule M
- Old Schedule M vs. Revised Schedule M
- Key focused area in revised Schedule M
- Revised Schedule M Contents- Part I: Good Manufacturing Practices for Pharmaceutical Products; Main Principles
- Revised Schedule M: Part II to Part XIII
- Challenges with the Schedule M compliance

Background for Revised Schedule M

- Draft of revised Schedule M was published by GOI, on 9th October 2018 for suggestions.
- Post evaluation of suggestions from stakeholders, Indian Regulatory Authority CDSCO notified the revised "Schedule M" on 28th Dec 2023.
- The objective is harmonisation of quality standards with global regulatory requirements (WHO Geneva, PIC/s etc.)
- Currently, there are around 10,500 drug manufacturing units in India. Of these, only 2,000 units comply with World Health Organisation's GMP guidelines.
- The revised standards will help many small and medium companies to compete in Export markets as well as Stringent Regulated Markets.
- Revised version is designed on a risk-based approach methodology with more emphasis is given to the Quality Risk Management principles and assessments.
- Specific requirements of GMP are mentioned in Schedule M, based on the product categories.
- Extensive trainings were conducted by CDSCO for the awareness and compliance of Schedule M throughout the country.

Implementation dates for Revised Schedule M (Indian drug regulations)*

- ❖ MSME (T/O < 250 Cr) - July'24
- ❖ Large Companies (T/O > 250 Cr) - Dec 24

* *Reference notified schedule M last page*

Impact of non-compliance against revised Schedule M (1/2)

Over 100 SMEs in Telangana plan to shut down due to incapability in upgrading to Revised Schedule M

Peethaambaran, Chennai
Wednesday, July 24, 2024, 08:00 Hrs [IST]

Finding that it will not be commercially viable to exist even after they are upgraded to the higher level of quality standards as per the Revised Schedule M norms, over 100 pharma MSMEs in Telangana are planning to shut down their manufacturing facilities in the next three months, according to IDMA Telenagana state president J Rajamouli.

He said all the large players have already complied with the quality standards. However, he did not divulge details about the units that have upgraded the technologies and which are the ones that plan to close down. The deadline for the small players to implement the new Schedule M ends in December this year.

"For upgrading to the New Schedule M, each unit has to invest Rs. 5 to 10 crore. But, if a minimum of Rs. 50 crore turnover per annum is not there, they cannot afford to operate. Commercially this much turnover is very difficult for the small players, so they are shutting down their units", Rajamouli said.

Answering questions from Pharmabiz, Rajamouli said he led a team of industry leaders to the office of the director general of the drugs control administration last month to request him to go slow in his inspection activities. According to sources, the officials of the department of drugs control are inspecting the facilities every day pulling the industries into trouble. The companies wanted sufficient time for fulfilling all the requirements. He said the DG has assured the industry association that the department will not hold inspections till the end of December 2024, the deadline mandated by the drug controller general of India. However, when the time limit is over the DC will start conducting inspections in all the units and there will not be any compromise on his part in complying with the requirements.

According to Rajamouli, the DCGI is unlikely to give extension for the SMEs to upgrade their units. This shows one fact that all the units under the MSME sector have to implement the new Schedule M norms within the timeframe given by the government if they want to exist.

He said all over Telangana there are 250 drug formulation units working at present. Out of this, except the major players, 50 per cent have already started compliance work and they will complete it at the end of this year. Ten unviable units were given Stop Production Orders, but they have not shut down yet. Last month the department issued show-cause notices to 20 companies, but soon they have rectified the anomalies and complied with the requirements. Following this, the industry leaders met the DG and made a request to stop the inspections for the time-being. The DG said he will cancel the licences of the companies which are found not complying with the new GMP after December this year.

According to CDSCO, out of the 400 manufacturing units inspected, 36 per cent of them have been forced to shut down because of non-compliance with quality standards. Out of the closed units none is likely to restart their operations because of non-viability. From every state in India, the respective state branch of the manufacturers association has requested the CDSCO to extend one year more time to fulfill the requirements. But it is learnt that the DCGI is not in favour of extending the deadline.

https://www.pharmabiz.com/NewsDetails.aspx?aid=171452&sid=1

Impact of non-compliance against revised Schedule M (2/2)

CDSCO Along With State Drugs Controllers Conducted Risk-Based Inspections Of 400 Premises Including MSMEs: JP Nadda

Written By : Ruchika Sharma | Medically Reviewed By : Dr. Kamal Kant Kohli

Published On 3 Aug 2024 2:00 PM | Updated On 6 Aug 2024 12:26 AM

CDSCO along with State Drugs Controllers conducted risk-based inspections of 400 premises including MSMEs: JP Nadda (medicaldialogues.in)

- Central Drugs Standard Control Organization and State Drugs Controllers have conducted risk-based inspections of 400 premises, including MSMEs, based on criteria such as number of drugs declared as Not of Standard Quality, complaints and criticality of products.
- Based on the findings of inspector more than 300 actions like
  - Issuance of show cause notice, Stop production order
  - Suspension and cancellation of licenses/ products

  have been taken by state licensing authority (SLA).

- 6 % of the total 400 units, in the pharmaceutical sector had closed their operations in the state by June end due to their failure to upgrade to new Schedule M norms in the absence of adequate funds.
- In Himachal, out of 655 pharma units, 255 are WHO-GMP certified and also have European Union-GMP and other international certifications like from the USFDA.
- The remaining 400 units working under the existing Schedule M rules are supposed to upgrade as per the revised GMP norms till December end or else could face closure as well.

Unable to upgrade, 144 pharma units in Himachal Pradesh close operations

Ambika Sharma Solan, July 16 As many as 144 micro, small and medium enterprises (MSME), 36 per cent of the total 400 units, in the pharmaceutical sector had closed their operations in the state by June end due to their...

TRIBUNE NEWS SERVICE

Updated At : 01:23 PM Jul 17, 2024 IST

https://www.tribuneindia.com/news/himachal/unable-to-upgrade-144-pharma-units-in-state-close-operations-640531/

Indian suppliers:
Incidences reported due to non-compliance of Good Manufacturing practices (1/3)

Year	Company	Incidence	Action by the authority/company
Feb-24	Genomix Pvt Ltd	The Drugs Control Administration (DCA) of Telangana unearthed an illegal manufacturing unit of an anti-cancer drug 'Cyclophosphamide Injection' at Indian Genomix Pvt Ltd, Cherlapally. Officials said that the company is manufacturing cytotoxic anti-cancer drugs together with antibiotic injections posing serious risk to public health	Investigation is on-going.
Jul-23	Magtech Enterprises	Fake diabetes medicines and multivitamins bearing the names of renowned pharmaceutical companies of Mankind and Intas Pharma.	The medicines worth Rs 55 lakh bound for Delhi were confiscated. Investigation is on-going.
Jun-23	Bharat Biotech	Recall typhoid vaccine due to its poor quality. India's Central Drugs Standard Control Organization declared a batch of Typbar typhoid vaccine "not of standard quality" (NSQ) after it failed standard testing. According to health officials, the levels of a particular molecule – O-acetyl – did not comply with national specifications. So, product was recalled from Indian markets.	Vaccine was exported to 50 countries, but there seem to be a problem of only one batch in India. There were no reports of adverse events or safety issues due to this batch in the country. There is no report about recall from other countries.
19-20	Digital vision	12 children died in 2019 after consuming contaminated cough syrups.	Digital says there was no DEG in its syrup and its medicines are not to blame. No action against drugmaker.
Feb-23	Global Pharma	The company recalled its eye drop from the US after it was linked to a drug-resistant infection. The eye drop has been linked to 55 incidents of infections, loss of vision, and even death due to the infection entering the bloodstream.	The FDA had recommended the recall due to manufacturing violations, including lack of appropriate microbial testing, formulation issues (the company manufactures and distributes ophthalmic drugs in multi-use bottles, without adequate preservatives), and lack of proper controls concerning tamper-evident packaging. Though one alleged death case is associated with the incident, no further information is available in the public domain.
Feb-23	Sun Pharma	The company recalled over 34,000 bottles of Diltiazem Hydrochloride extended-release capsules in the US after they failed the quality test.	A Class II recall is initiated by USFDA. In this situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

Indian suppliers:
Incidences reported due to non-compliance of Good Manufacturing practices (2/3)

Year	Company	Incidence	Action by the authority/company
Feb-23	Galentic Pharma	The company recalled all its tetracycline hydrochloride ointment batches from 2020 till February 2023. This WHO Medical Product Alert	Investigation is on-going. No further information is available at WHO site.
Nov-22	Aurobindo Pharma	The company recalled 9,504 bottles of Quinapril and Hydrochlorothiazide tablets due to manufacturing lapses.	N-Nitroso Quinapril impurity was found in the product. Risk assessment of nitrosamine impurities must be performed prior to commercialization. This could have serious patient impact . Aurobindo Pharma, initiated the class-II voluntary recall on 5th October this year.
Sep-22	Aurobindo Pharma	The company recalled 11,520 units of Fondaparinux Sodium Injection in the US market.	The company initiated the class-II recall for the affected lot across the US
Feb-23	Maiden Pharmaceuticals	A Sonipat court sentenced two pharmaceutical company executives of Maiden Pharmaceuticals to two-and-half years in jail for exporting substandard drugs to Vietnam a decade ago	Criminal action against the offenders.
Nov-22	Emcure	The company recalled a batch of the iron supplement infection Orofer FCM	The FDA issued an order asking Pune-based Emcure to recall its product Orofer following the death of a 55-year-old man in Mumbai. Emcure pleaded not guilty and arguing spurious drug case. No further information is available in public domain.
Nov-22	Nixi Lab	As many as 75 patients, who had undergone surgeries at Haryana were administered Propofol injection, of whom 11 had suffered from “adverse reactions” from the use of anesthetic from Nixi Laboratory Four patients had recovered from the adverse reactions, while “six” had died.	The company refuted the charges and claimed incidences could have happened due to mishandling by the anesthetists. As per public domain information FIR could not be filed. But more details to be obtained.
2015	GSK biosciences	EU bans 700 generic drugs for manipulation of trials by GVK Biosciences An inspection by the European Medicines Agency uncovered instances of "data manipulation of electrocardiograms (ECGs)" in certain generic medicine studies, which appeared to have taken place over a period of at least five years,"	EU drug regulator recommended that marketing authorisation of these drugs should be suspended as they were based on clinical trial data allegedly manipulated by the Hyderabad- based company.

Indian suppliers:
Incidences reported due to non-compliance of Good Manufacturing practices (3/3)

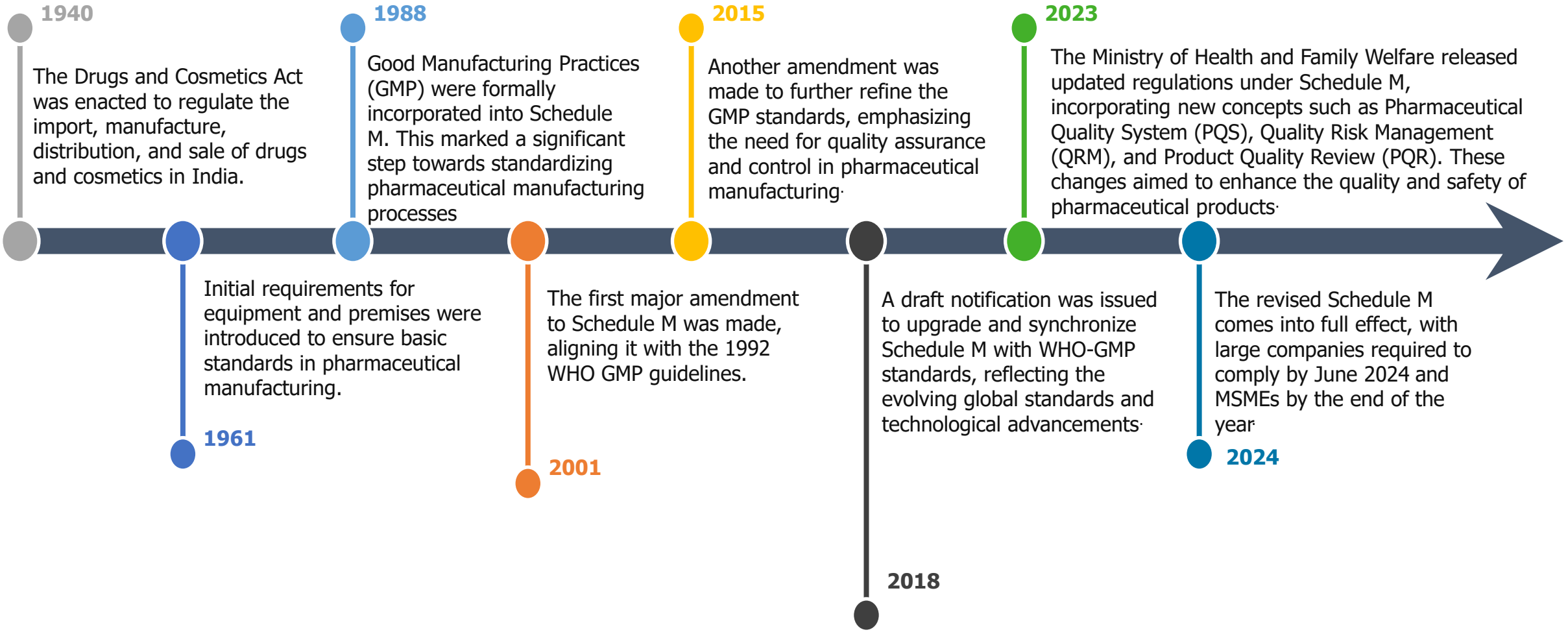
Year	Company	Incidence	Action by the authority/company
2014	39 Indian drug companies blacklisted by Vietnam	Companies blacklisted by Vietnam including Aurobindo Pharma, Cadila and Macleods Pharmaceuticals have been blacklisted by Vietnam for quality standard violations. Major players such as Strides Arcolab Ltd, Medley Pharmaceuticals Ltd, Marck Biosciences Ltd, Marksans Pharma Ltd and UMedica Laboratories Pvt Ltd are in the list. Antibiotics made by Aurobindo and Macleod, and Cadila's anti-rabies vaccine Lyssavac have been banned. Apart from the Indian companies, nine from Korea , two from Bangladesh, two from France, and one each from the US, Philippines, Pakistan, Russia, Indonesia, Germany, Cyprus, and Canada have been banned.	Representative of banned companies stated that problem is with retail storage. The Central Drugs Standard Control Organization (CDSCO) carries out routine checks across the country through its zonal offices. Every month, it issues a list of NSQ drugs.
Nov-13	Sandoz	Sandoz, has pulled two batches of tuberculosis drugs from the Indian market after some packages were found to have improper doses in strips of medications. Authorities say they were alerted by a Mumbai doctor who said a patient had a reaction to the improper dose. The drugs were packaged in strips that contain one tablet that is a combo of rifampicin and isoniazid, two tablets of pyrazinamide and one tablet of ethambutol. A Mumbai doctor notified India's FDA that some of his patients had bought packages at a pharmacy in which the strips contained two of the combo tablets. He told authorities one patient began vomiting after getting 5 strips into his regimen with the improper dosage.	Sandoz confirmed that the product was manufactured at Themis Medicare at Haridwar
2013	Ranbaxy Laboratories Ltd.	US subsidiary of major Indian drug manufacturer Ranbaxy Laboratories Ltd. pleaded guilty to US federal criminal charges and agreed to pay $500 million for selling adulterated generic drugs, fabricating data, and committing fraud.	Ranbaxy also agreed to pay a criminal fine and forfeiture totaling $150 million and to settle civil claims under the False Claims Act and related State laws for $350 million.
22-23	Marion Biotech Product name: Ambronol and DOK-1 Max.	In Uzbekistan, deaths of 68 children after allegedly consuming contaminated cough syrup in December 2022.	The license of the company was cancelled on December 30, 2022, by the Indian authorities Later, permission to make products using propylene glycol (PG) is cancelled, and it is allowed to make and sell all other products, provided it submitted CAPA plan. An Indian national, along with 22 others, were jailed by an Uzbekistan court for a period of 2-20 years.

SCHEDULE M:

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR PHARMACEUTICAL PRODUCTS

- Schedule M is a set of guidelines and requirements laid down by the Central Drugs Standard Control Organization (CDSCO). It falls under the Drugs and Cosmetics Act, 1940, and its associated Rules.
- It is designed to ensure that pharmaceutical manufacturing processes adhere to strict Good Manufacturing Practices (GMP).
- The standards laid down by Schedule must be mandatorily followed by pharmaceutical manufacturers.
- Schedule M applies to all types of drugs and pharmaceuticals manufactured in India, including:
  - Allopathic medicines
  - Ayurvedic, Siddha, and Unani medicines
  - Biological products
  - Homeopathic medicines
  - Medical devices
  - Radiopharmaceuticals
  - Vaccines

Evolution of Schedule M



Old Schedule M vs. Revised Schedule M

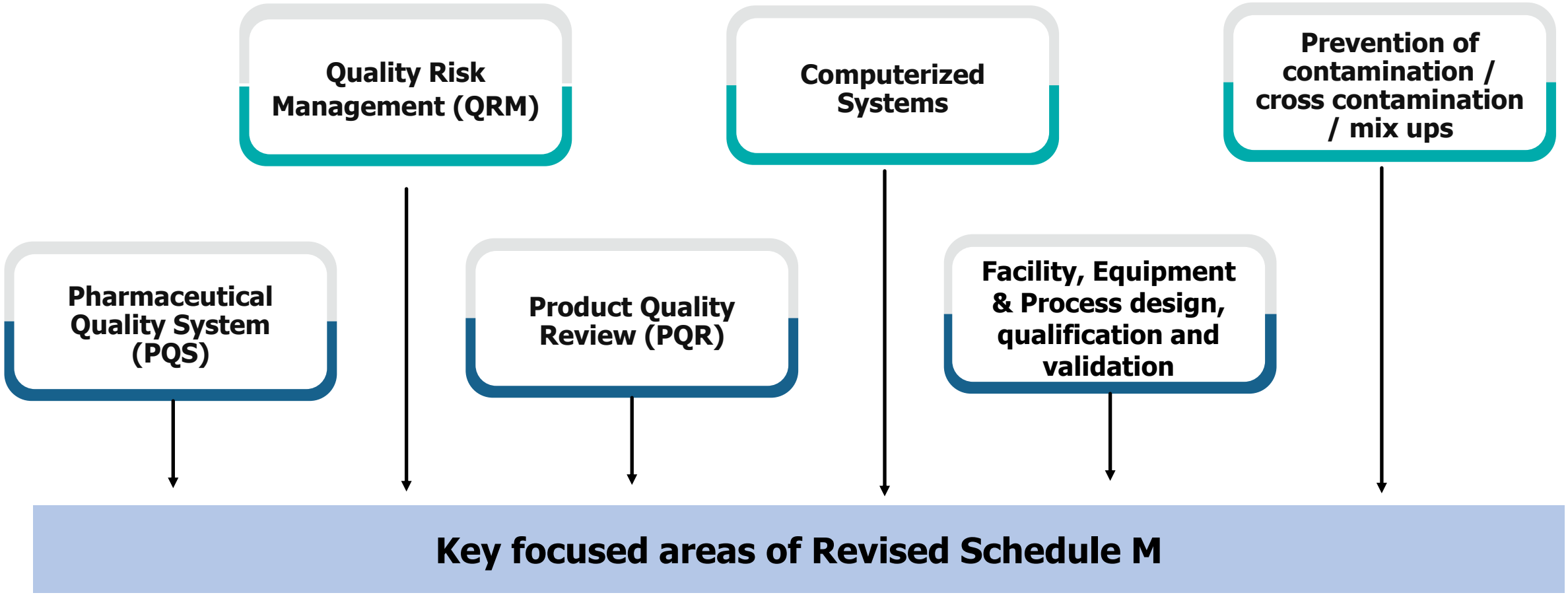
Old Schedule M

- Schedule M of 2001 is divided in two parts.
- Part I : General Manufacturing Practices for Premises and Materials Each section is explained with certain requirements but not in specific details. Subparts are Part IA to Part IF Deals with GMP for Specific product Types.
- Part II- Requirements of Plant and Equipment
  - External Preparation
  - Oral Liquid Preparation
  - Tablets
  - Powders
  - Capsules
  - Ophthalmic Preparation
  - Pressurizers & Suppositories
  - Inhalers & Vitrallae
  - Repacking of drugs & pharma chemicals
  - Parenteral Preparation

Revised Schedule M

- Schedule M of 2018 is divided in XIII Parts
- Part I- Good Manufacturing Practices for Pharmaceutical Products
  - Part I is termed as "Main Principles" & it is mandatory to follow irrespective of product category.
  - An Appendix I which deals with requirements of Site Master File.
- Part II to Part XII
  - Specified requirements for manufacturing, as per product categories. E.g. Sterile products, hazardous substances, Oral Solid dosage Forms etc.
  - Five new categories are added as compared to existing Schedule M
- Part XIII
  - Requirements of plant and equipment for manufacturing of 11 categories of pharma products.
  - This section is similar as of previous schedule M 2001.

Key focused areas in Revised Schedule M



Revised Schedule M Contents- Part I:
Good Manufacturing Practices for Pharmaceutical Products; Main Principles

1	Pharmaceutical Quality System	14	Premises
2	Quality Risk Management	15	Equipment
3	Good Manufacturing Practices for Pharmaceutical Products	16	Materials
4	Sanitation and Hygiene	17	Reference Standards
5	Qualification and Validation	18	Waste Materials
6	Complaints	19	Documentation
7	Product Recalls	20	Documents Required
8	Change Control	21	Good practices in Production
9	Production under loan licence or contract and contract analysis and other activities	22	Good practices in Quality Control
10	Self-Inspection, Quality Audit, Supplier Audit and approval	23	Computerised Systems
11	Personnel	Appendix- I - Site Master File	
12	Training	Part I- "Main Principles", it is mandatory to comply for all types pharmaceutical products manufacturing.	
13	Personnel Hygiene		

Part I: Main principles
Good manufacturing practices for pharmaceutical products (1/4)

#	Sub-section	High-level overview
1	Pharmaceutical quality system (PQS)	• PQS is a comprehensive framework designed to ensure the quality of pharmaceutical products throughout their lifecycle. • Senior management responsibility to ensure that effective pharmaceutical system to be defined and implemented.
2	Quality risk management (QRM)	• Evaluation of risk is based on scientific knowledge, process experience, and patient protection. • Applicable both proactively and retrospectively. • More emphasis on periodic product quality review.
3	Good manufacturing practices for pharmaceutical products	• GMP involves clearly defined manufacturing processes, systematic risk reviews, qualification and validation, adequate resources (including qualified personnel, appropriate premises, equipment, materials, and procedures), clear instructions, thorough record-keeping, effective storage and distribution, and a system for product recall and handling complaints. • Records must be maintained to show compliance with defined procedures, deviations must be investigated, and corrective actions must be implemented.
4	Sanitation and hygiene	• A high level of sanitation and hygiene must be practiced in all aspects of drug manufacturing. • The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and anything that could become a source of contamination to the product
5	Qualification and validation	• Responsibility for validation must be clearly defined, conducted according to approved protocols, and results documented in written reports. • Special attention is required for validating analytical test methods, automated systems, and cleaning procedures. • Key elements of qualification and validation is Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Process Validation (PV) or Performance Qualification (PQ)
6	Complaints and adverse reaction	• All complaints about potentially defective products must be reviewed and addressed according to written procedures, with corrective actions and possible recalls as needed. A designated person with supporting staff is responsible for handling complaints and informing the authorized person.

Part I: Main principles
Good manufacturing practices for pharmaceutical products (1/4)

#	Sub-section	High-level overview
7	Products recalls	• A system must be in place to recall defective products from the market, with an authorized person responsible for executing and coordinating the recalls • Written procedures for recalls must be established, regularly reviewed, and updated, including secure storage of recalled products and timely communication with licensing authorities and stakeholders. • Distribution records should be accessible, including detailed information for effective recall, with progress monitored, documented, and evaluated periodically for effectiveness.
8	Change control	• Establish a formal change control system for evaluating changes in production and product control, with written procedures for approval and documentation. • Proposals for changes must be drafted, reviewed, and approved by relevant organizational and quality units, with an evaluation of their impact on product quality and classification (major or minor) for appropriate testing and validation. • Implemented changes require updated documentation, evaluation of the first batch produced under the change, and assessment of potential impacts on retest or expiry dates, with possible inclusion in stability programs if necessary.
9	Production under loan licence or contract and contract analysis and other activities	• Production under loan license or contract and contract analysis must be clearly defined, agreed upon, and controlled to ensure quality and prevent misunderstandings. • Contracts should cover technology transfer, product quality systems, and include detailed terms for activities, responsibilities, and handling of rejected products. • The loan licensee or contract giver must ensure the provider's competence, review records, and monitor performance. The manufacturing facility provider or contract acceptor must maintain standards, avoid unauthorized changes, and not subcontract without approval.

Part I: Main principles
Good manufacturing practices for pharmaceutical products (2/4)

#	Sub-section	High-level overview
10	Self-inspection, quality audits and suppliers, audits and approval	• Self-inspections should be routine and also conducted during special circumstances like recalls or regulatory inspections, with a documented procedure and effective follow-up. • Written instructions must cover essential GMP aspects, including personnel, premises, equipment maintenance, storage, production controls, QC, documentation, sanitation, validation, calibration, recall procedures, complaints management, labels control, and results of previous inspections. • A self-inspection team of GMP experts, appointed by management, must conduct inspections at least annually. Reports should include results, evaluations, conclusions, and corrective action recommendations, with follow-up evaluations by management. • Quality control is responsible for approving suppliers based on their ability to meet specifications and GMP standards.
11	Personnel	• Adequate and qualified personnel must be employed, with clearly defined and documented responsibilities. Responsibilities should not overload individuals to avoid compromising quality, and all personnel should be effectively trained in good manufacturing practices (GMP). • Heads of production and quality units, including the **authorized*** person, must have relevant qualifications and experience. They are responsible for authorizing procedures, monitoring quality, validating processes, and ensuring compliance with GMP. • The release of products can be delegated to **qualified individuals*** who must follow approved procedures. Key responsibilities include ensuring all checks, validations, and documentation are completed and reviewed.
12	Premises	• Detailed requirement for premises including production area, weighing area, ancillary area, storage area, quality area, equipment, material and quality control area. More emphasis on prevention of contamination / cross contamination / mix ups.
13	Equipment	• Specific requirements are mentioned for equipment Design and Maintenance, Installation and Labeling, Calibration and Cleaning, Handling Defective Equipment, and Documentation.

** FDA approved person*

Part I: Main principles
Good manufacturing practices for pharmaceutical products (3/4)

#	Sub-section	High-level overview
14	Materials	• Materials Handling and Storage: Materials, including starting and packaging materials, must be quarantined upon receipt and stored under conditions that ensure batch segregation and stock rotation. Water used in manufacturing must meet quality standards and be stored appropriately. • All materials must be checked for integrity and compliance with specifications upon arrival. Labels must include essential details such as batch numbers, status, and expiry dates. Only materials approved by QC and within their shelf-life should be used. • Packaging materials must be stored securely and handled according to strict procedures to avoid mix-ups. Rejected or recalled products should be marked, stored separately, and either reprocessed or destroyed after proper evaluation.
15	Reference standard	• Official reference standards should be used as specified in their respective monographs. • Standards prepared by the manufacturer must be tested, released, and stored similarly to official standards and kept in a secure area under a designated person's responsibility. • Reference standards must be labeled with the name, batch or lot number, date of preparation, shelf-life, potency, and storage conditions. Secondary or working standards must be tested and standardized periodically to ensure accuracy and reliability.
16	Waste management	• Waste, including toxic and flammable materials, must be stored in designated, secure areas and removed regularly for safe disposal. Disposal of sewage and effluents must comply with Environmental Pollution Control Board guidelines, and bio-medical waste must be destroyed per the Bio-Medical Waste (Management and Handling) Rules, 2016. • Rodenticides, insecticides, fumigants, and sanitizers must not contaminate equipment or materials, ensuring no adverse effects on products.
17	Documentation (GDP)	Good documentation practices (GDP) is essential part of Pharmaceutical operations and a vital part of Quality assurance. This section documented the specific requirements, not limited to, for batch manufacturing records, packaging records, testing procedures, quality specifications, etc. GDP will support the release/reject decision for a particular batch for sale ensuring the traceability of operations and data generated as per design of processes.

Part I: Main principles
Good manufacturing practices for pharmaceutical products (4/4)

#	Sub-section	High-level overview
18	Good practices in production	• Production operations must follow clearly defined procedures in accordance with manufacturing and licenses, with the objective of obtaining products of the requisite quality. • Prevention of cross-contamination and bacterial contamination during production • Processing Operations**:** Ensure work areas and equipment are clean before starting; conduct in-process and environmental controls; withdraw defective equipment from use; clean production equipment immediately after use; check connections and sanitize water pipes; service and calibrate equipment regularly; prevent hazards during repair and maintenance. • Packaging Operations**:** Minimize cross-contamination and mix-ups; clean packaging areas and equipment before use; display product name and batch number; label immediately after filling and sealing; verify printing and labeling accuracy; use roll-feed labels where possible; perform regular online checks; handle unusual packaging events with special inspection; investigate discrepancies in packaging materials and batch counts; destroy unused batch-coded materials; review production records and investigate any batch failures before release.
19	Good practices in quality control	• 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. • Stability shall be determined prior to marketing and following any significant changes e.g. changes in in-process, equipment or packaging materials.
20	Computerised systems	• GMP-related computerized systems must be validated based on their complexity and criticality, including installation and operational qualifications. Existing systems lacking initial validation may undergo retrospective validation. Controls must prevent unauthorized data access, changes, and omissions, with records maintained for any data modifications. • Adequate data back up system would be necessary to ensure that there no permanent loss of data due to failure of system.

Revised Schedule M: Part II to Part XIII

Specific Requirements for Manufacturing of Pharmaceutical Products

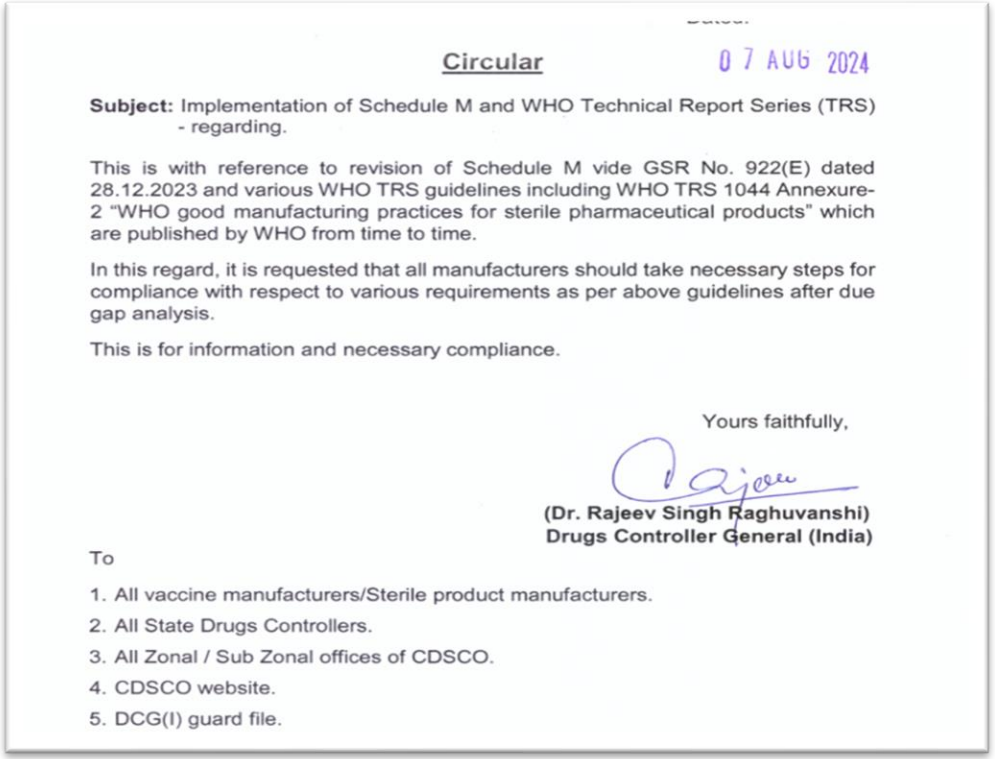
Part II to Part XIII

Part II	Specific requirements for manufacture of Sterile Products, Small & Large Volume Parentals, Ophthalmic Preparations -
Part III	Specific requirements for manufacture of Hazardous substances such as Sex Hormones, Steroids or Cytotoxic substances (Newly Added)
Part IV	Specific requirements for manufacture of Biological Products (Newly Added)
Part V	Specific requirements for manufacture of Radiopharmaceutical Products (Newly Added)
Part VI	Specific requirements for manufacture of Phytopharmaceutical Products (Newly Added)
Part VII	Specific requirements for manufacture of Investigational Pharmaceutical Products for Clinical Trials in Human (Newly Added)
Part VIII	Specific requirements for manufacture of Oral Solid Dosage Forms -
Part IX	Specific requirements for manufacture of Oral Liquids-
Part X	Specific requirements for manufacture of External Preparations
Part XI	Specific requirements for manufacture of Metered Dose-Inhalers
Part XII	Specific requirements for manufacture of Active Pharmaceutical Ingredients-
Part XIII	Specific requirements for premises, plants & equipments

Part II: Specific requirements for manufacture of sterile products, parenteral preparations (small volume injectables and large volume parenterals) and sterile ophthalmic preparations

Schedule M -2001	Schedule M Notified 28 Dec 2023
Requirements have been provided in Schedule M but without 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 **TRS 1044 - Annex 2: WHO good manufacturing practices for sterile pharmaceutical products.**

To ensure Sterility Assurance throughout the manufacturing process by designing a facility wide contamination control strategy (CCS)



Circular

07 AUG 2024

Subject: Implementation of Schedule M and WHO Technical Report Series (TRS) - regarding.

This is with reference to revision of Schedule M vide GSR No. 922(E) dated 28.12.2023 and various WHO TRS guidelines including WHO TRS 1044 Annexure-2 "WHO good manufacturing practices for sterile pharmaceutical products" which are published by WHO from time to time.

In this regard, it is requested that all manufacturers should take necessary steps for compliance with respect to various requirements as per above guidelines after due gap analysis.

This is for information and necessary compliance.

Yours faithfully,

(Dr. Rajeev Singh Raghuvanshi)
Drugs Controller General (India)

To

1. All vaccine manufacturers/Sterile product manufacturers.
2. All State Drugs Controllers.
3. All Zonal / Sub Zonal offices of CDSCO.
4. CDSCO website.
5. DCG(I) guard file.

Part III:
Newly added part for hazardous substances applicable for API and FDF both

Specific requirements for manufacturing of pharmaceutical products containing hazardous substances such as sex hormones, steroids (anabolic, androgenic) or cytotoxic substances

Schedule M dated 2001	**Current Schedule M dated Dec 2023**
• 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
	WHO Technical Report Series, No. 957, 2010 Annex 3 and revised Schedule M part III are **identical**.
	Barrier technology: A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a **barrier isolator (BI)** or a restricted access barrier system (RABS)

Part IV to VII: Newly added parts

Part	Schedule M dated 2001	Current Schedule M dated Dec 2023
Part IV: Specific requirements for manufacture of biological products	There are currently no separate regulations detailing specific requirements for the manufacturing of the following categories: • Biological products • Radiopharmaceutical products • Phytopharmaceuticals • Investigational pharmaceutical products for clinical trials in humans.	Comprehensive and separate provisions for the specific requirements regarding the manufacture of the following products • Biological Products • Radiopharmaceutical Products • Phytopharmaceuticals • Investigational Pharmaceutical Products for Clinical Trials in Humans.
Part V: Specific requirements for radiopharmaceutical products		
Part VI: Specific requirements for phytopharmaceuticals		
Part VII:Specific requirements for the manufacture of investigational pharmaceutical products for clinical trials in humans		

Part VIII: Specific requirements for manufacture of oral solid dosage forms (tablets and capsules)

Schedule M dated 2001	Current Schedule M dated Dec 2023
Requirements has been provided in schedule M	Detailed guidelines on pressure cascade systems, airlocks, and humidity control, including specific types of airlocks (cascade, sink, bubble) and their applications.
	Detailed instructions on pressure differentials, cascade regimes, and specific types of airlocks (1.1 to 1.25).
	Added detailed requirements on controlling and monitoring temperature and relative humidity, with specific provisions for different humidity control systems (1.27 to 1.34).
	New sections on dust extraction and air filtration with specific requirements for dust collectors and filters (1.39 to 1.60).
	No major changes in sifting, mixing, granulation, compression, coating, and packaging.

Part IX: Specific requirements for manufacture of oral liquids (syrups, elixirs, emulsions and suspensions)

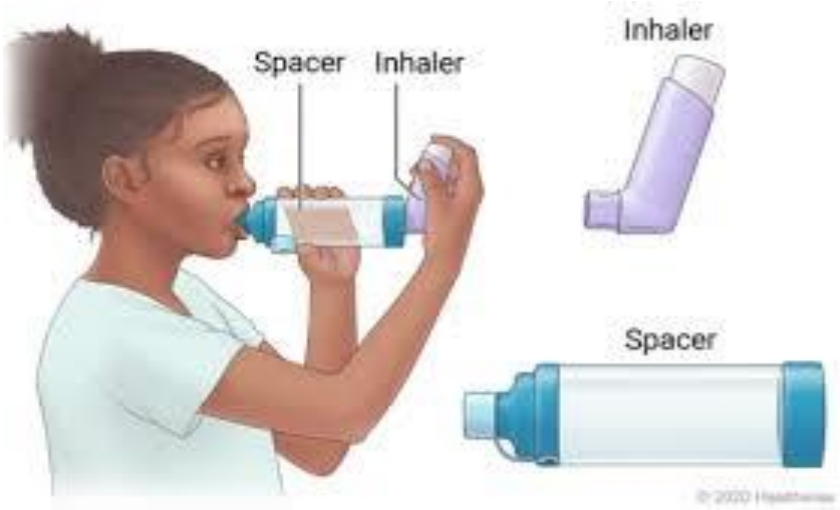
Schedule M dated 2001	Current Schedule M dated Dec 2023
Requirements has been provided in schedule M	Processing: Closed systems of processing and transfer recommended. Effective ventilation with filtered air for exposed products or clean containers.
	Primary Packaging Area: Revised filter specification to "level-3 filters" with detailed filter types and classifications based on air systems (e.g., EN779 G4 plus F8 plus EN1822 H13 filtres)

Part X: Specific requirement for manufacturing of Topical products i.e., External preparations (creams, ointments, pastes, emulsions, lotions, solutions, dusting powders and identical products)

Schedule M dated 2001	Current Schedule M dated Dec 2023
Requirements has been provided in schedule M	Primary, Secondary, and Tertiary Filters: The requirement includes EN779 G4 plus F8 plus EN1822 H13 filters.
	The new regulations simplify the air filtration requirement from "at least 20 air filters" to "suitable filters" and require an HVAC system.

Part XI: Specific requirements for manufacture of metered–dose– inhalers (MDI)

Schedule M dated 2001	Current Schedule M dated Dec 2023
Requirements has been provided in schedule M	Revised regulation introduces detailed descriptions of the two common manufacturing methods: • Two-shot system (pressure filling) • One-shot system (Cold filling)
	HVAC system should be in place
	Added specific requirement for Leakage test: Test shall be performed in a way which avoids microbial contamination or residual moisture.



Part XII: Specific requirements for manufacture of Active Pharmaceutical ingredients

Schedule M dated 2001	Current Schedule M dated Dec 2023
Requirements has been provided in schedule M.	It integrates Good Manufacturing Practices (GMP) for APIs, ensuring that these standards are applied to every stage from raw material receipt to API release
	It provides more scope, covering APIs manufactured through various methods, including chemical synthesis, fermentation, and extraction from natural sources. It excludes certain products like vaccines and blood derivatives, giving it a broader range of API-related processes.
	Detailed instructions are provided for in-process sampling, blending of batches, and quality assurance. These include stricter documentation and procedural requirements for deviations, reprocessing, and reworking of APIs

Challenges with the Schedule M compliance

Small and medium drugmakers seek two year extension on revised Schedule M norms

Updated - August 26, 2024 at 09:06 PM. | Mumbai

Deadline for them to adhere to the revised Good Manufacturing Practices (GMP) norms was December 2024

DCC asks states and UTs to ensure implementation of revised Schedule M as per timelines

Gireesh Babu, New Delhi
Thursday, September 12, 2024, 08:00 Hrs [IST]

ETPrime

Pharma companies seek more time to implement revised norms on manufacturing practices

By ET Bureau • Last Updated: Aug 26, 2024, 12:38:00 AM IST

FOLLOW US SHARE FONT SIZE SAVE

Ensure Compliance Of Revised Schedule M: DCGI To All State/ UT Drug Controllers (06-08-2024)

New Delhi, 6 Aug 2024: *Dr. Rajeev Singh Raghuvanshi, Drugs Controller General (India)* has written to All State/ UT Drug Controllers that the Central Government has amended the Drugs Rules, 1945 vide G.S.R. 922(E) dated 28.12.2023 regarding 'Good manufacturing practices a.....

SIDVIM Lifesciences can help you comply with Schedule M guidelines..

SIDVIM Quality Team (1/2)

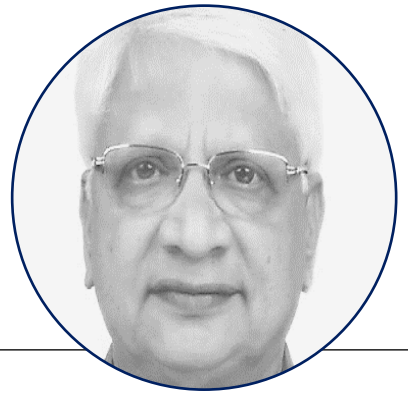
Dr. Pavan Gajare

Expertise: 20+ yrs.

- Quality assurance for FDF and API for multiple Indian Co.
- Specialized in analytical testing, lab documentation, quality protocols, GMP and GLP standards for Indian and stringently regulated markets.

Last Experience:
Asst. Manager QA - Rubicon Research

Educational Qualification:
PhD. in Chemistry (Jaipur National University)



Chandrashekhar Deo

Expertise: 45+ yrs.

- Specialized in quality policy formation, validation, qualification, technical transfers, technical training.
- Conducted over 200 quality audits for Novartis group of companies.

Last Experience:
Quality Head at Sandoz

Educational Qualification:
Bachelors in Chemistry

Dr. Yimraj Chirmade

Expertise: 35+ yrs.

- Specialized in audit and GMP compliance, regulatory permissions & licenses.
- Experienced in domains of QC, QA, product development, process validation and contract manufacturing.

Last Experience:
Head Q.A. Com Ops-Sandoz Private Limited

Educational Qualification:
M.Sc., Ph.D.

Padmini Dalal

Expertise: 30+ yrs.

- Specialized in quality compliance, quality infrastructure, microbiology – formation of systems and infrastructure, tech transfer.

Last Experience:
Regional Quality Head at Sandoz

Educational Qualification:
Masters in Microbiology (University of Mumbai)

SIDVIM Quality Team (2/2)

Satyajit Kokatay

Expertise: 35+ yrs.

- Specialized in Computer systems validation.
- Experienced in quality control systems, stability testing, equipment qualification and managing TP location and tech transfer compliance.

Last Experience:
Quality at Johnson & Johnson

Educational Qualification:
MS in Chemistry

Surya Namburi

Expertise: 20+ yrs.

- Successful regulatory submissions of multiple formulations and medical devices in domestic, ROW, EU & US markets.
- Experience in conducting quality audits for formulations & medical devices.

Last Experience:
Head – Regulatory Affairs at Biocon Pharma

Educational Qualification:
Masters in Pharmaceutics

Vivek Nagle

Expertise: 30+ yrs.

- Specialized in audit and GMP compliance.
- Experienced in domains of QC, QA, product development, process validation and contract manufacturing.

Last Experience:
Sr. Manager – QC at Oman Pharmaceutical Products

Educational Qualification:
Bachelors in Chemistry (University of Mumbai)

Amaiyya Agarwal

Experience: 2 yrs.

- Market analysis, business analysis, & data analytics.

Last Experience:
Business Development Intern at Impact Guru

Educational Qualification:
MBA in Pharma Tech & Healthcare Management (NMIMS)

Thank You!

We welcome questions! For more information please contact:
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Amaiyya Agrawal: amaiyya.agrawal@sidvim.com

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