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A REVIEW ARTICLE ON AN EXISTING SCHEDULE M VS REVISED SCHEDULE M

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ABSTRACT: Schedule M is considered as an important part in the Drugs and Cosmetics Act 1940, Rules 1945. For making a product with proper quality and effective for the human beings it is necessary to maintain or follow the guidelines of schedule M. Schedule M is considered as the guidelines which talks mostly about Good Manufacturing Practices. Schedule M was first established in the year 2001 and it was divided into Part 1 and Part 2. Then in the year 2018 it was divided into 12 Parts more precisely than first one which was established in the year 2001. Then in the year of 2024 it became more precise, and it was divided into 13 Parts and including the changes introduced in, the revised Schedule M which include introduction of a Pharmaceutical Quality System (PQS), Quality Risk Management (QRM), Product Quality Review (PQR), Qualification and Validation of Equipment, and a Computerized Storage system for all drug products. These revised Schedule M will help in making the product proper and effective to the human beings. The revised Schedule M makes it easy for the identification of the risk and to check whether the product is maintaining quality system or not. The revised Schedule M will make the records of the documentation for future references. Schedule M is a crucial part for all the manufacturing products used by the human. Previous Schedule M doesn't give much explanation about each topic which creates problems most of the time. It is better to be revised.

INTRODUCTION: Schedule M is the set of guidelines or regulations which mainly deals with the good manufacturing practices for the pharmaceutical products [1, 2]. It is the part of Drugs and Cosmetics act 1940, rules 1945. It is being followed by all the manufacturers for making a good therapeutic product for the human beings. The products which are made by following the rules or guidelines is effective.

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It is a part of quality assurance system which tells that the products are consistently manufactured, and quality standards appropriate to their intended use. The new schedule M has 13 parts. The existing schedule M only focuses on the good manufacturing practices, but the revised schedule M put a special focus on the premises, plants and equipment with the addition GMP requirements.

In addition, they also focus on the Product quality review (PQR), Pharmaceutical quality system (PQS), Quality risk management (QRM), Qualification and validation of equipment and computerized storage system for all products. It also focuses on the risk management and self-inspection. This will help in producing the drug's safety, quality and efficacy [5, 6]

The revised schedule is more specific to the topic and helps in manufacturing a product with good quality, and effective. As we know that schedule M is the vital part and it is followed by the manufacturers minutely [3, 4].

History: Good manufacturing part of Drugs and Cosmetics Act 1940, was first incorporated in Schedule M of the Drugs and Cosmetics Act & Rules, in the year 1988 and the last amendment was done in June, 2005, deals with Good Manufacturing Practices for pharmaceuticals that should be followed by pharmaceutical manufacturing units in India [7, 8]. Schedule M guides on Good Manufacturing Practices regarding company premises, quality control system, quality check laboratories, production, cleaning of equipment, housekeeping, cross-contamination, and other related topics.

On the last year of 28th December 2023, the revised schedule M was implemented which mostly focuses on the quality management system of the pharmaceutical product [10, 11].

Salient Features:

OLD Schedule M: Schedule M was first divided into 2 parts:

Part 1:

- ✓ Good Manufacturing practices for the premises and materials.
- ✓ It also had a subpart starting from 1A to 1F.

Part II:

- ✓ Requirements of Plant and Equipment:
- External Preparations.
- Oral Liquid Preparations
- Tablets
- Powders
- Capsules
- Surgical Dressing
- Ophthalmic Preparations
- Pressurizes and suppositories
- Inhalers and vitrallae
- Repacking of Drugs and Pharmaceutical Chemicals
- Parenteral Preparation

Proposed Schedule M: Schedule M was divided into 12 parts:

Part I: Good Manufacturing Practices for Pharmaceutical Products.

- ✓ Part I is completely different.
- ✓ This 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.
- ✓ 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.

New Schdeule M: Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products

Part I:

- ✓ Pharmaceutical Quality system
- ✓ Quality Risk Management
- ✓ Good Manufacturing practices for pharmaceutical products.
- ✓ Sanitation and Hygiene

- ✓ Qualification and Validation.
- ✓ Complaints and Adverse Reaction
- ✓ Product Recall
- ✓ Change Control
- ✓ Production under loan license or contract and contract analysis and other activities.
- ✓ Self-inspection, quality audits and supplier audits and approval
- ✓ Personnel
- ✓ Premises
- ✓ Equipment
- ✓ Materials
- ✓ Reference standards
- ✓ Waste materials.
- ✓ Documentation
- ✓ Good practices in production
- ✓ Good practices in quality control
- ✓ Computerized system

Appendix -1: Site master file.

Part II to Part XII:

- ✓ 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 VII 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 Ingredient.

Part XIII:

1. Requirements of Plant and Equipment for External Preparations.
2. Requirements of Plant and Equipment for Oral Liquid Preparations.
3. Requirements of Plant and Equipment for Tablets.
4. Requirements of Plant and Equipment for Powders.
5. Requirements of Plant and Equipment for Capsules.
6. Requirements of Plant and Equipment for Surgical Dressing.
7. Requirements of Plant and Equipment for Ophthalmic Preparations.
8. Requirements of Plant and Equipment for Pessaries and Suppositories.
9. Requirements of Plant and Equipment for Inhalers and Vitrallae.
10. Requirements of Plant and Equipment for Repacking of Drugs and Pharmaceutical Chemicals.
11. Requirements of Plant and Equipment for Parental Preparation.

New Schedule M Principles:

Pharmaceutical Quality System (PQS): It is a part of pharmaceutical Management system in a pharmaceutical Industry. Pharmaceutical quality system should be applied to the product starting from the manufacturing of the product to the dispatch of the product to the market [13]. In every manufacturing company the senior management responsibility is to implement an effective PQS in the company. The finished product should be checked and confirmed then only they are dispatched. The CAPA (Corrective action and preventive action) should be maintained so that any problem is there with the product then it can be identified by the root cause analysis so that the problem does not occur in the future [15].

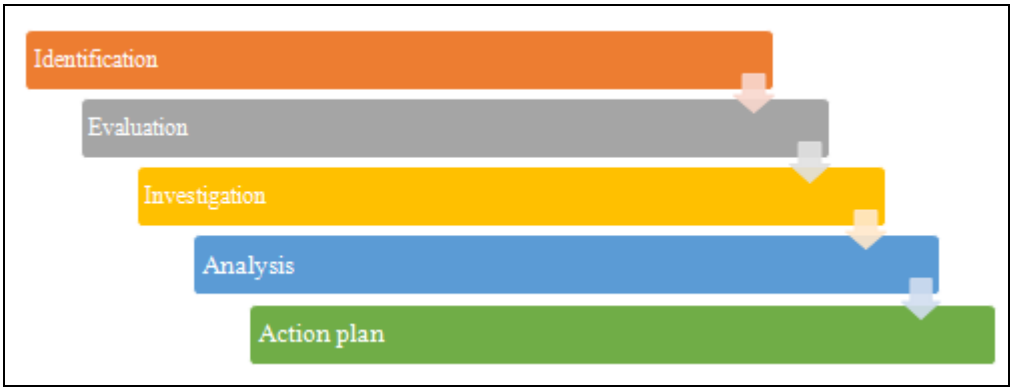

FIG. 1: FLOW CHART OF CAPA PROCESS

There should be also quality risk management for identifying the risk. Any defect, deviations or other problems should be reported, investigated and recorded. The self- inspection or audit should be done in each step so that the mistake can be overcome [17].

The aim of the Pharmaceutical Quality Management System (QMS) is to guarantee and uphold consistent and superior quality in the manufacturing of pharmaceutical products through an all-encompassing set of guidelines, protocols, and practices [18].

Quality Risk Management: It is the specific tool to assess the risk or the defects associated with the manufacturing of the product and drug substances. If we can overcome the risks associated with the product then we can provide a quality product [17].

There is always some danger involved in the production and use of medication (medical) products, including their constituent parts. The whole risk consists of more than just the risk to its quality.

It's critical to realize that good risk-based decision-making throughout the product lifetime ensures that the qualities critical to the medication (or medicinal) product's quality are preserved and that the product continues to be safe and effective [16].

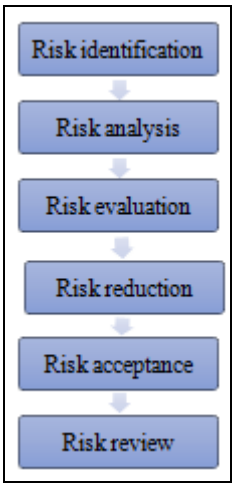

FIG. 2: FLOW CHART OF RISK IDENTIFICATION PROCESS

Product Quality Review: It is necessary to carry out rolling, periodic, or regular quality reviews of all pharmaceutical items. Check that the quality parameters and product process are consistent. Based on the quality review report, the manufacturer should determine whether re-validation or the relevant CAPA is required. CAPAs must be finished on time and include an ongoing evaluation of their efficacy [14].

In addition to making sure the data is accurate, the person in charge of product release should make sure the quality review is finished in the allotted time. Every year, product quality reviews must be carried out and recorded [13].

Every annual review report must also take into account all of the prior reviews.

The report should address a few of the following topics, but not all of them:

- ✓ Examination of the product's raw components and packaging materials.
- ✓ Examining the traceability of active ingredients in the supply chain.
- ✓ Examination of crucial process controls and final product outcomes a study and inquiry of every batch that didn't match the specified specifications.
- ✓ An examination of all modifications made to the procedures or analytical techniques.
- ✓ An examination of the filed, approved, or rejected dossier variations.
- ✓ An analysis of the stability monitoring program's findings and any unfavorable patterns.

Sanitation and Hygiene: Strict standards of hygiene and sanitation must be followed in all facets of the pharmaceutical manufacturing process. The scope of hygiene and sanitation should include Employees, Facilities, Containers, Production Materials, Equipment and Cleaning and Disinfecting Products. Anything that comes into contact with the merchandise [15]. It is necessary to remove any potential sources of contamination. There should be a sanitization and hygiene program in place. Wash hands with soap and water [13]. The dress should be clean or else it would cause cross contamination to the product. The personnel who are involved in the manufacturing industry should be free from any kind of diseases.

The Qualification and Validation: The updated schedule M lists more precise requirements than the previous one did. The equipment, instruments, processes, and procedures that the company wants qualified and validated should be identified. There should be a validation master plan in place outlining the essential components of validation and qualification program [14]. It is actually used to establish and proof design Qualification (DQ), installation qualification, performance qualification (PQ) / process, operations qualification (OQ), and qualification (IQ) verification (PV). Re-qualification and re-validation requirements must be specified precisely [15]. The accountability for carrying out validation activities needs to be specified explicitly. Special consideration must be given to the validation of automated systems, analytical test methodologies, and methods for cleaning. It is also playing an important role in manufacturing of the product [16].

Production under Loan License or Contract and Contract Analysis and Other Activities: One of Schedule M's most significant additions. To prevent quality problems, activities carried out under a specific arrangement and covered by GMP should be precisely defined, agreed upon, and crucially controlled. The following tasks, including but not limited to tech transfer, supply chain, subcontracting validation, batch releasing authorization, changes or changes resulting from incidents or errors, quality control, in-process controls, *etc*., should be covered by a quality contract or agreement [19].

Continual the vendor's contract acceptor conducting an audit of the site(s) should be cognizant of all the hazards related to the product, work, or tests that could endanger persons, property, equipment, *etc*. Competent individuals with the necessary understanding of process technology, analysis, and good manufacturing practices should develop the contract's technical provisions.

Computerised System: Very significant section regarding the regulatory agencies' present strategy. The qualification, validation, review, and data management related to computerized systems are covered in detail in this section. Validation needs to be grounded in the system's complexity, diversity, and criticality. Any modifications to the electronic system must follow a change procedure with upholding and approving each and every record. These documents will show that the system is kept up to date and validated [18]. There must be a backup system in place to ensure that documents are never permanently lost because of failure or collapse of the system. Computerized systems must be equipped with sufficient safeguards against unwanted access or modifications to the data.

Waste Materials: Waste materials must be stored properly and safely in a designated area. It is necessary to properly segregate waste materials from one another. Combustible and toxic products must be stored in appropriately designed, independent, closed cabinets. The removal of solid, liquid, and gaseous effluents and sewage. The manufacturing area must adhere to the specifications of Board for Environment Pollution Control. All biomedical waste needs to be eliminated in accordance with the guidelines of the Biomedical Waste Products. Fumigating agents, insecticides, rodenticides, and sanitizing supplies not allowed to contaminate tools, supplies for starting, materials used in packaging, manufacturing processes, or final goods. Waste materials should be put in the dustbin for the better use.

TABLE 1: COMPARISON BETWEEN SCHEDULE M AND REVISED SCHEDULE M

S. no.	Point	Existing	Updated
1	Sanitation	It covers only workers/ manufacturing premises	It covers personnel, equipment, production materials, manufacturing area, containers, closure systems
2	Qualification/ Validation	It covers only manufacturing process, testing and cleaning	It covers premises, utilities and equipment.
3	Product Recall	There was no provision to inform the LA.	Should be informed to LA, Comprehensive system specifies for prompt and effective recall.
4	Compliance and Adverse drug reaction	Serious adverse drug reactions	This includes faulty manufacturer, product deterioration, serious quality problems.
5	Change control	Only in case of significant change	This covers changes in specifications, analytical methods, facilities, utilities, equipment, labeling and packaging
6	Production	No details of contract giver, acceptor was required	This covers the roles and responsibilities of contract giver, acceptor agreement.
7	Self-inspection/ quality audit/ supplier audit/ approval	Routinely performed and also in specific occasion, i.e. during recall and during third party inspection	At least once a year, supplier audit and approval
8	Materials	-	Validated computerized storage system. Identify test for each container except dedicated facilities, reworking of rejected products- new batch number, part of earlier batches into a batch of the same product at defined stage of manufacturer. Extension of retest date.
9	Reference standard	-	IP RS/IS procured from IPC procedure for working standard.
10	Documentation	Master Formula Record (MFR), Standard Operating Procedure (SOP) in hard copy for verification	Audit trail to ensure existence of documented evidence, traceability, MFR- hold time permitted for intermediates and in-process materials.
11	Sterile products	Requirement has been provided in schedule M but without reference to latest requirement.	Separate comprehensive provisions on specific requirements
12	Hazardous materials, hormones, steroids, cytotoxic	No separate provision about requirement for manufacturing of such product however segregated/isolated production areas within building with different AHU and pressure differential	Separate comprehensive provisions on separate requirements.
13	Biological,V-Radiopharmaceutical, clinical trials	No such separate provision about requirement for manufacturing of such product	Separate comprehensive provisions on separate requirements.
14	Pharmaceutical Quality system (PQS)	No section in existing schedule M	Newly added. Specific requirements are mentioned separately
15	Quality Risk Management	Not mentioned in existing schedule M	Separate section for risk management systems

CONCLUSION: It is concluded that the new or the existing schedule M is very useful for the pharmaceutical industry in manufacturing a product. The existing schedule M is fully explained

than the revised schedule M. Existing Schedule M had 12 parts but the new schedule M is 13 parts and it is more precise. As we know that schedule M mostly talks about good manufacturing practices. Existing schedule M doesn't include the requirements of the radiopharmaceuticals, phyto-pharmaceuticals, investigational Pharmaceutical products used in the clinical trials. Proper schedule m will help in making a good pharmaceutical product along with maintaining a safety, quality and efficacy.

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