Regulatory expectations for Quality Compliance-
Proposed revisions of Schedule M

Chandrashekar Ranga
Deputy Drugs Controller (India)
Central Drugs Standard Control Organization

Centre Starts Probe After WHO Claims Indian Cough Syrups Behind 66 Deaths In The Gambia

WHO had highlighted that a significant contributing factor to the deaths was suspected to be the use of medicines that may have been contaminated with Diethylene Glycol/Ethylene Glycol, and said its presence had been confirmed in some of the samples it tested.

Healthcare & Pharmaceuticals | Drug & Device Trials | Regulatory | Climate Change

U.S. FDA says India-made eye drop linked to some infections, blindness and one death

Reuters

February 3, 2023 11:54 PM GMT+5:30 · Updated 8 months ago

Drugs Survey
NSQ and Spurious Drugs Data - Source wise*

RETAIL OUTLETS	Spurious: 0.0237%	NSQ: 3%
GOVT. SOURCES	Spurious: 0.0597%	NSQ: 10.02%
PORTS(IMPORTS)	Spurious: NIL	NSQ: NIL

National Average*

(Retail, Government Sources and Ports)

Spurious: 0.0245%

NSQ: 3.16%

*Statistical Analysis by ISI, Hyderabad

Details of RBI carried out

Sr. No.	States	Total Inspections	No. of RBI
1	Himachal Pradesh	654	80
2	Punjab	181	7
3	Haryana	194	6

Regulatory Expectations

- Compliance labelling claim
- Efficacy similar to the reference product
- Patient Safety
- Data to support the claims
- Consistency of the quality
- Quality Systems
- Regulatory compliance
- Others

Common observations during RBI

- Food supplements manufactured in the same premises
- Lack of facilities for the products licensed
- Lack of measures to prevent cross-contamination
- HVAC system absent or not adequate or not working
- Water system not validated
- Raw materials and finished goods not tested
- Poor microbiology lab facilities
- Analytical method not validated
- Lack of consistent batch size
- Lack of R & D/Poor product understanding during formulation

Common observations during RBI-2

- Lack of dedicated section for potent products
- Parenteral products
  - Hold time study
  - Media fill
  - Failing in sterility
- Issues of Data integrity
- No root cause analysis
- Lack of vendor qualification
- Lack of SOPs or failure to follow SOP
- Lack of freedom to the Technical Staff

A CAPA WITHOUT ROOT CAUSE ANALYSIS

Issues to be addressed

- Multi product manufacturing facility
- Batches not produced regularly
- Bioavailability/bioequivalence studies
- Concept of formulation development
- Quality Culture at all levels
- Continuous training
- Data integrity

Data Integrity (probably the very GMP ground)

- The term "**Data Integrity**" refers to requirements for complete, consistent, and accurate information (data)
- Data should be Attributable, Legible, Contemporaneously recorded, Original or a true copy, and Accurate (ALCOA, there is even an ALCOA+ approach)
- The concept of data integrity underpins GMPs and is a requirement for paper based & electronic record keeping and the use of electronic signatures

Cf. WHO TRS 996, 2016, Annex 5

Learn to trust your team, don't be a micro-manager

Delegate Effectively, But Give Them Freedom To Fail Too

By Tarun Rai

I had the honour last month to deliver the convocation address at IIM-Calcutta. It struck me that as the over 500 freshly minted MBAs take their first steps into their careers, they are confronted with an amazing pace of technological change. Most recently led by 'generative AI' — ChatGPT, Midjourney, Stable Diffusion, etc. Technology that will replace jobs and, at the very least, change the nature of jobs.

I have been working now for the past 35 years. A career that started in sales & marketing at Asian Paints but then turned to advertising & media. I was lucky to be heading an independent profit centre by the age of 36. And become a CEO at 43. Over the years, I have worked with and mentored a lot of youngsters. I have seen many of them do exceedingly well in their careers, while some stagnated. I have my own experience of joining my current company at the junior-most position and rising to be its CEO.

So, here's my advice on what it takes to be a successful professional: Energy, curiosity, agility, conviction, trust, resilience, empathy. And here is a bonus: Humour.

▶ **Energy:** Do you get to work with positivity and excitement? A smile on your face, a song in your heart? Do you sit at your desk all day or do you move around meeting people? Yes, literally. Energy is infectious. Energy can transform the dynamics of a team, of an office. Energy spurs action. No, it doesn't mean one has to be boisterous, but it does mean being passionate and letting people know it.

▶ **Curiosity:** Curiosity didn't kill the cat. Without curiosity, you will get dated very quickly. Be like a sponge. Soak up learning from everyone you interact with. Be a voracious reader. Sign up for online courses.

▶ **Agility:** In a fast changing world, you need to be agile. Be ready to unlearn to learn. There are no holy cows. The past is no barometer of the future. You can't race ahead looking at the rear-view mirror.

▶ **Resilience:** In trying new things, you will fail. That's ok. But fail fast, learn fast. Pick yourself up and try again.

In a fast changing world, leaders need to be agile. They should be ready to unlearn to learn. In the new era, domain knowledge will also need to be refreshed frequently. Leaders should also be more curious or risk getting dated quickly

▶ **Trust:** Don't be a micro-manager. Learn to trust your team. Only then can you delegate effectively. Give your team the freedom to fail.

▶ **Empathy:** Empathy is 'the ability to understand and share the feelings of another person'. What are the motivations of the people you are dealing with? What are the challenges your team members are facing? Professional and personal. Understanding them is the key to making them realise their potential and be more productive.

▶ **Conviction:** I have seen people without a strong point-of-view on anything. They agree easily. With their colleagues and with their clients. They follow a path of least resistance. Soon, nobody cares for what they think. Don't be stubborn, but it is important to have conviction.

▶ **Humour:** Humour is a great stress-buster. It relieves tension in pressure situations. Humour breaks barriers. I can say it from experience and with a lot of confidence that this is, possibly, the most underrated of traits in the corporate world.

Domain knowledge will continue to be important, but it is not a differential — it's table stakes. In the new era, domain knowledge will also need to be refreshed frequently.

(The writer is former executive director — APAC, Wunderman Thompson)

- **Management responsibility is essential** to establish and maintain a *company commitment to Quality Policy* and for the performance of the Pharmaceutical Quality System.

- Senior Management should commit formally to follow the Quality Policy
- Quality should be the responsibility of ALL involving field staff to senior / upper management
- *Responsibilities that should NOT be delegated*

Relationships of Quality

Specifications
Sampling
Testing

Personnel
Training
Validation
Self inspection

Quality Manual
Quality objectives

Quality System
Quality Policy
QRM.

Why do need revision of Schedule M

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

Components of GMP(existing)

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

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

Critical Components of GMP

Ventilation System - HVAC

To provide

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

What is achieved:

- To avoid contamination
- To ensure quality

Pharmaceutical Water

Low Quality Water:

- Product degradation
- Product contamination
- Seasonal and regional variation

Types of water contaminant

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

Stability Studies

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

- Temperature
- Humidity
- Light

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

- Meet Regulatory Requirements / Product Registration.

Comparison Between Existing Schedule M And Draft Upgraded Schedule M

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

Pharmaceutical Quality System

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

1. Pharmaceutical Quality System

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

2. Quality Risk management

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

3. Good Manufacturing Practices

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

Aim:

Managing and Minimizing Risk

4. Sanitation

Existing :

Covers only Workers and manufacturing premises

New:

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

5. Qualification and Validation

Validation:

Existing:

Covers only manufacturing process, testing and cleaning

New:

Also covers Premises, Utilities and equipment

Qualification:

Existing: No provision

New:

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

6.Compliance and Adverse reactions

Existing:

- Serious Adverse drug reactions reported to Licensing Authority

New:

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

7. Product Recall

Existing:

- No provision to inform to LA

New:

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

8.Change Control

Existing:

- only in case of significant changes

New:

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

9.Production

Existing:

No details of Contract giver, contract acceptor, Contract analysis

New:

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

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

Existing:

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

New:

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

11.Personnel

New:

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

12.Premises

Detailed requirements about premises including

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

13. Equipment

- Validated Cleaning procedures

14.Materials

New:

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

15.Reference Standard

New:

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

16.Waste Materials

- By and large similar provisions

17. Documentation

Exist:

- MFR, SOP in hard copy for verification

New:

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

18. Good Practices in Production

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

19. Good Practices in Quality Control

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

20. Computerised Systems

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

Applicability of WHO Guidelines

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

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

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

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

iv. GMP guidelines for validation.

v. Guidelines on packaging of pharmaceutical products

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

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

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

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

Summary

- Quality is a Continuum Process
- Quality does not end when a batch is release
- Quality is not only about generating stacks of documents to satisfy regulators
- Quality is a state of mind that starts in development, but maintain throughout the life cycle of the product

Thank you