Comparison of Guidelines of

Indian GMP with WHO GMP

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Comparison of Guidelines of Indian GMP with WHO GMP

Outline of Presentation

- **Introductory Elements**
- **Section wise Comparison of Indian GMP withWHO GMP**
- **Web of Schedule M**
- **Discussion on Significant Differences**
- **Conclusion - spirit of 'Make in India'**

Comparison of Guidelines of Indian GMP with WHO GMP

Reference

Indian GMP, SCHEDULE M

- Drugs and Cosmetics Act 1940
- Drugs and Cosmetics Rules 1945
- Schedule L1
- Schedule U

WHO GMP

- WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles, Annex – 2, WHO Technical Report Series 986, 2014

Comparison of Guidelines of Indian GMP with WHO GMP

Implementing Authority

Indian GMP, SCHEDULE M	WHO GMP
• Drugs Control Administration (DCA) of each state And Central Drugs Standard Control Organization(CDSCO) as Central License Approving Authority (CLAA) for special category of drugs.	• State Drugs Control Administration (DCA) and Central Drugs Standard Control Organization(CDSCO) through joint inspection of the facility.

Comparison of Guidelines of Indian GMP with WHO GMP

Historical Background

Indian GMP, SCHEDULE M

- GMPs prescribed under Schedule M vide GSR 735 (E) dt.24th June, 1988
- While reviewing the case of large volume parenterals, National Human Rights Commission (NHRC) recommended to bring the Schedule M to the level of international texts.
- Schedule M revised on par with WHO-GMP text, vide notification no.GSR 894 (E) dt.11th December, 2001.
- Applicable to all the drug manufacturing units in India w.e.f. 1-7-2005.

WHO GMP

- First draft on WHO GMP prepared in 1967. (resolution WHA 20.34)
- Revised text in 1971, (Annex. to 22nd report)
- First version of WHO certificates scheme (resolution WHA 22.50)
- Revised version of both certification scheme & GMP text in 1975 (resolution WHA 28.65)
- Revised draft of WHO-GMP presented in three parts in 1992 (WHO-TRS-823)
- cGMP published as Annex. 3 in WHO TRS No.961, 2011.
- Further revised and published on TRS No.986, 2014

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Main Requirements

Indian GMP, SCHEDULE M

Schedule M, Part-I : Good Manufacturing Practices for Premises and Materials

1. General Requirements
2. Warehousing area
3. Production area
4. Ancillary area
1. Quality control area
2. Personnel
3. Health, clothing & sanitation of workers
8. Manufacturing operations and controls
9. Sanitation in the manufacturing premises
10. Raw materials
11. Equipment
12. Documentation and records
13. Labels and printed materials
14. Quality assurance
15. Self inspection and quality audit

WHO GMP

- WHO good manufacturing practices for pharmaceutical products: main principles - Annex 2, WHO Technical Report Series 986, 2014

1. Pharmaceutical quality system
2. Good manufacturing practices for pharmaceutical products
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers audit and approval

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Main Requirements (Contd..)

Indian GMP, SCHEDULE M

•Schedule-M, Part-I: (contd…)

16. Quality control system
17. Specification
18. Master formula records
19. Packaging records
20. Batch packaging record
21. Batch processing record
22. Standard operating procedures
23. Reference samples
24. Reprocessing and recoveries
25. Distribution records
26. Validation and process validation
27. Product recalls
28. Complaints and adverse reactions
29. Site master file

WHO GMP

•WHO good manufacturing practices for pharmaceutical products: main principles - Annex 2, WHO Technical Report Series 986, 2014 (contd…)

9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment
14. Materials
15. Documentation
16. Good practices in production
17. Good practices in quality control

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Specific Requirements

Indian GMP, SCHEDULE M	WHO GMP
• Part-IA: specific requirements for manufacture of Sterile Products • Part-IB: specific requirements for manufacture of Oral Solid Dosage Forms • Part-IC: specific requirements for manufacture of Oral Liquids • Part-ID: specific requirements for manufacture of Topical Products • Part-IE: specific requirements for manufacture of Metered Dosage Inhalers • Part-IF: specific requirements for manufacture of Active Pharmaceutical Ingredients	• WHO good manufacturing practices for Sterile Pharmaceutical Products, Annex 6, TRS961, 2011 • Pharmaceutical Excipients, Annex 5, TRS 885, 1999 • Biological Products, Annex 3, TRS 822, 1992 • Active Pharmaceutical Ingredients (bulk drug substances), Annex 2, TRS 957, 2010 • Water for Pharmaceutical use, Annex 2, TRS 970, 2012 • WHO good manufacturing practices for Blood Establishments (jointly with the Expert Committee on Biological Standardization), Annex 4, TRS 961, 2011.

Comparison of Guidelines of Indian GMP with WHO GMP

Specific Requirements (Contd..)

Indian GMP, SCHEDULE M

- Part-II: Requirements of Plant & Equipment

1. External Preparations
2. Oral Liquid Preparations
3. Tablets
4. Powders
5. Capsules
6. Surgical Dressing
7. Ophthalmic Preparations
8. Pessaries & Suppositories
9. Inhalers & Vitralle
10. Repacking of drugs and pharmaceutical chemicals
11. Parenteral Preparations

WHO GMP

- WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms , Annex 5, TRS 961, 2011
- Validation . Annex 4. TRS 937. 2006
- Guidelines on good manufacturing practices: validation, Appendix 7, on-sterile process validation , Annex 3, TRS 992, 2015
- Risk analysis Application of Hazard Analysis and Critical Control Point (HACCP) Methodology in Pharmaceuticals, Annex 7, TRS 908, 2003
- WHO guidelines on transfer of technology in pharmaceutical manufacturing, Annex 7, TRS 961, 2011
- Training materials

Quality Control laboratory training modules

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Section wise Comparison

Indian GMP, SCHEDULE M

1. GENERAL REQUIREMENTS

1.1. Location and surroundings:
To avoid risk of contamination from external environment.

2.Building and premises: Designed, constructed, adapted and maintained to suit the manufacturing operations under hygienic conditions. Shall confirm the conditions under Factories Act 1948.

- **(i) Compatible.**
- **(ii) Adequately provided with working space.**
- **(iii) Prevent entry of insects etc.**

WHO GMP

12. Premises
1.Principle. Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.
General
12.2. The layout and design of premises must aim to minimize the risk of errors on the quality of products.
3.Measures should be taken to avoid cross-contamination.
4.Premises should be situated in an environment with measures to protect risk of causing any contamination of materials.
5.Facilitate good sanitation.
6.Ensured that repair and maintenance operations do not hazard to the quality of products.

Comparison of Guidelines of Indian GMP with WHO GMP

Section wise Comparison (Contd..)

Indian GMP, SCHEDULE M	WHO GMP
GENERAL REQUIREMENTS 1.2. Building and premises: iv. Proper AHU for maintaining temperature & humidity suitable to the comforts of the people working. v. Provided with drainage system. vi. The walls & floor be free from cracks; smooth workable.	12. Premises 12.7. Premises should be cleaned according to written procedures. 8.Electrical supply, lighting, temperature, humidity and ventilation should be appropriate during manufacture and storage. 9.Designed and equipped, against the entry of insects, birds or other animals. 10.Designed to ensure the logical flow of materials and personnel.
1.3 Water System: Validated Water System.	14. Materials 14.6. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Comparison of Guidelines of Indian GMP with WHO GMP

Section wise Comparison (Contd..)

Indian GMP, SCHEDULE M	WHO GMP
1.4. Disposal of waste: (i) Conformity with requirements of Environment Pollution Control Board. (ii) Bio-medical waste shall be destroyed as per Bio-medical Waste (Management and Handling) Rules, 1996. (iii) Additional precautions for rejected drugs. (iv) Disposal of Hazardous, Toxic substances and flammable materials in conformity with Central and State Legislation.	Waste materials 14.44 Provision for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation. 14.45 Waste material should not be allowed to accumulate
2. Warehousing Area: 2.1. Designed to allow sufficient and orderly warehousing of various categories of materials and products.	Storage areas: 12.15. Sufficient capacity to allow orderly storage of materials.

Comparison of Guidelines of Indian GMP with WHO GMP

Section wise Comparison (Contd..)

Indian GMP, SCHEDULE M	WHO GMP
2. Warehousing Area:	Storage areas:
2.2 To ensure good storage conditions.	12.16. Designed or adapted to ensure good storage conditions.
2.3 Receiving and dispatch bays.	12.17 Receiving and dispatch bays should be separated.
2.4. Quarantine status – any system with equivalent assurance.	12.18 Quarantine status must be clearly marked.
2.5 Separate sampling area for active raw materials and excipients.	12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials.
2.6 Segregation for rejected, recalled or returned materials .	12.20 Highly active and radioactive materials, narcotics, other dangerous medicines should be stored in safe and secure areas.
2.7 Hazardous, poisonous, explosive etc. stored in safe and secured areas, in conformity of concerned Civic Authority.	12.21. Printed packaging materials safe and secure storage.
2.8. Printed packing materials in safe, separate and secure areas.	

Comparison of Guidelines of Indian GMP with WHO GMP

Section wise Comparison (Contd..)

Indian GMP, SCHEDULE M	WHO GMP
2. Warehousing Area: 2.9. Separate dispensing areas for special categories of products. 2.10 Sampling & dispensing of sterile materials in grade A. 2.11 Regular checks against spillage, breakage and leakage of containers. 2.12 Regular Pest control treatment.	Storage areas: 12.22. Separate sampling area for starting materials. Weighing areas 12.23. Weighing of starting materials and estimation of yield in separate weighing areas.
3. Production area: 3.1 To allow Production in uniflow. 3.2 Separate, dedicated self-contained facilities for penicillins or biological preparations with live microorganisms. Beta-Lactum, sex hormones and cytotoxic substances.	Production areas 12.24 Minimize the risk of a serious medical hazard due to cross contamination 12.25 Production areas connected in a logical order corresponding to the sequence of the operation.

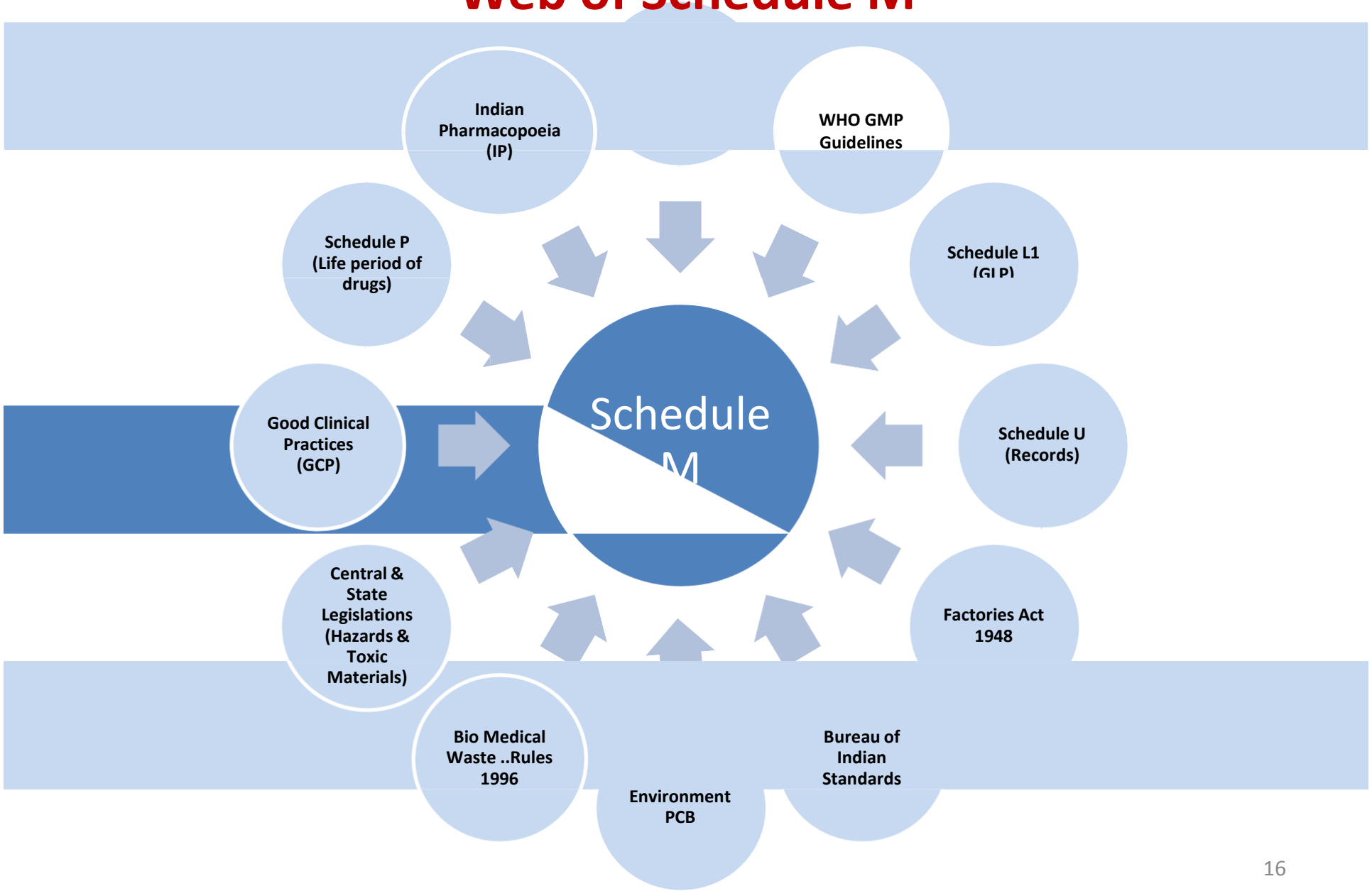
Comparison of Guidelines of Indian GMP with WHO GMP

Section wise Comparison (Contd..)

Indian GMP, SCHEDULE M	WHO GMP
3. Production area:	Production areas
3.3 Working and in-process space.	12.26. Adequate working and in-process storage space.
3.4 Services lines by colours to avoid accumulation of dust & identified.	27. Materials exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks.
	28. Pipe work, light fittings, ventilation points should be designed and sited.
	29. Drains should be designed and equipped to prevent back-flow.
	30. Production areas should be effectively ventilated, with air-control facilities.
	31. Premises for the packaging of pharmaceutical products should be specifically designed.
	32. Production areas should be well lit.

Comparison of Guidelines of Indian GMP with WHO GMP

Web of Schedule M



Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences

Pre-Discussion note:

Directions for interpretation of Schedule M

1. **Note at the beginning of Part-I of Schedule M**

To Achieve the objectives listed below, each licensee shall evolve appropriate methodology, systems and procedures which shall be documented and maintained for inspectional reference; and the manufacturing premises shall be used exclusively for production of drugs and no other manufacturing activity shall be undertaken therein.

2. **Note at the beginning of each part (Part-1A to Part-1F) of Schedule M**

The general requirements as given in the part 1 of this schedule relating to requirements of good manufacturing practices for premises and materials for pharmaceutical products shall be complied with, *mutatis mutandis*, for the manufacture of the referred pharmaceutical products. In addition to these requirements the following specific requirements shall be followed.

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

1. The Stability Studies are referred under para 16.10, part-I of Schedule M.

It reads that the quality control department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of the storage. All records of such studies shall be maintained.

Under chapter 17 "Good Practices in Quality Control" subparts 17.22 to 17.25 and Annex-2, WHO TRS 953 refers stability testing of Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP), proposed criteria as mentioned below .

Climatic Zone	Long Term testing conditions	Accelerated
I	21 ºC /45% RH	40 ºC /75% RH
II	25 ºC /60% RH	40 ºC /75% RH
III	30 ºC /35% RH	40 ºC /75% RH
IVa	30 ºC /65% RH	40 ºC /75% RH
IVb	30 ºC /75% RH	40 ºC /75% RH

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

2. Para 1.3, Part-I of schedule M under the subheading **Water System** has the mention of "There shall be validated system for treatment of water…"

Under chapter 14 of *WHO GMP guidelines*,(TRS 986) under heading **Materials** the sub part 14.6 directs "Water used in the manufacture of pharmaceutical products should be suitable for its intended use".

And

Refers water for pharmaceutical use, Annex-2, WHO TRS 970, 2012

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

3. Para 2.5, Part-I of Schedule M under the subheading "**Warehousing Area**" has the mention of "There shall be a separate sampling area in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross-contamination and mix-ups".

Under chapter 12 "**Premises**" subchapter 12.22 "**Storage Areas**" of WHO GMP guidelines (TRS 986) reads "there should normally be a separate sampling area for starting materials (if sampling is performed in the storage area it should be conducted in such a way as to prevent contamination or cross-contamination)".

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

4. Para 3, part 1 of schedule M , sub-para 3.2 under heading **Production area** that "Separate dedicated facilities shall be provided for manufacture of contamination causing and potent products such as Beta-lactum, sex-hormones and cytotoxic substances.

Chapter 12.24 of WHO-GMP guidelines (TRS 986) under heading **Production area** require that "The production of certain highly active products such as antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products shall not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary Validation(including cleaning validation) are made.

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

5. Para 4.4, Part-I of Schedule M under the subheading **"Ancillary Areas"** has the mention of "Areas housing Animals shall be isolated from the other areas. The other requirements regarding the animal houses shall be those as prescribed in rule 150-C(3) of Drugs and Cosmetics Rules 1945, which shall be adopted for production purposes."

Under the chapter 12 **"Premises"** under the subheading 12.14 **"Ancillary Areas"** of WHO GMP guidelines indicates(TRS 986) that "Animal houses should be well isolated from other area, with separate entries (animal access) and air handling facilities".

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

6. Para 7.1 part-I of Schedule M under the subheading **"Health, clothing and Sanitation of Workers"** has the mention of "The personnel handling Beta-lactum antibiotics shall be tested for Penicillin sensitivity before employment and those handling sex hormones, cytotoxic substances and other potent drugs shall be periodically examined for adverse effects ".

   under the Chapter 11 "**Personal hygiene"** sub point 11.1 of WHO GMP guidelines (TRS 986) reads that "All Personnel, prior to and during employment, as appropriate, should undergo health examinations".

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

7. Para 8.1, part-I of Schedule M under the subheading Manufacturing operations and controls requires that "the products not prepared under ascetic conditions are required to be free from pathogens like Salmonella, Escherichia coli, Pyocyanea, etc..".

There is no such specific provision in WHO-GMP guidelines (TRS 986).

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

8. Para 10.9 , pat-I of Schedule M under the subheading "**Raw materials**" it has the mention of "It shall be ensured that the shelf life of formulation product shall not exceed with that of active raw materials used".

Under chapter 14.15 "**Starting Materials**" of WHO GMP guidelines(TRS 986) directs that "only starting materials released by QC department within their shelf life should be used".

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

9. Para 11, part 1 of Schedule M under sub para 11.4, under heading, **Equipment** it specifies that "To avoid accidental contamination where ever possible, non toxic/edible grade lubricants shall be used and the equipment shall be maintained in a way that lubricant do not contaminate the products being produced."

Under chapter 14.3, **General** of WHO GMP guidelines (TRS 986) specifies that "No materials used for operations such as cleaning, lubrication of equipment and pest control should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks".

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

10. Para 16 part 1 ,Schedule M, under sub-para 16.8 under heading, **Quality control system** specified that "Assessment record should be signed by the incharge of production and counter signed by the authorized Quality control personnel before a product is released for sale or distribution.

Under chapter 1, **Pharmaceutical quality system** sub chapter 1.5(i) prescribe that "Pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 and 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products".

Comparison of Guidelines of Indian GMP with WHO GMP

Discussion on Significant Differences (Contd…)

11. The Indian GMP, Schedule M is to be amended on par with WHO-GMP guidelines (TRS 986) to incorporate the following ;

    a) Pharmaceutical Quality System (PQS)
    b) Quality Risk management (QRM)
    c) Quality Management System (QMS)
    d) Suppliers Audit and Approval in Para 15 part-I of Schedule M under subtitle **"Self Inspection And Quality Audit"**
    e) Specification for testing procedure in para 17, Part-I of Schedule M under sub title **"Specification"**

Comparison of Guidelines of Indian GMP with WHO GMP

Conclusion

- On comparison of regulations of Indian GMP, Schedule M and WHO good manufacturing practices for pharmaceutical products, it is noticed that all the principal requirements of WHO GMP text are taken and incorporated into Indian GMP vide GSR no. 894(E) dated 11th December 2001

- In addition to the main principles of WHO GMP the Schedule M also invoked certain provisions of other related acts and rules which are relevant in the Indian context. Hence, the good manufacturing practices under Schedule M of the Drugs & cosmetics rule 1945 has to be read with other schedules of the D&C rules viz. Schedule U & Schedule L1 and other acts and rules viz. Factories Act 1948, Environment pollution control board rules, Biomedical Waste (Management & Handling) rules 1996, GCP, etc.

Comparison of Guidelines of Indian GMP with WHO GMP

Conclusion (Contd..)

- There is specific mention of certain important requirements in schedule M like separate sampling area for active raw materials and excipients. Separate dedicated facilities for Beta-lactum, Sex-hormones and Cytotoxic substances, etc. to prevent contamination and mix-ups effectively.
- While complying the WHO GMP requirements, the schedule M has incorporated additional requirements as per the Indian experience & legal status and thus found to be more stringent than the WHO GMP Guidelines.
- However the Indian GMP requires updating of the GMP requirements as per changing trends in GMP Globally. The chapters viz. Quality policy, Quality Risk management, concepts of Hazards of Critical and Control Point (HACCP), etc. are to be incorporated in the forthcoming amendments.

Thank You