HOW TO PRACTICE GMPs

Seventh Edition

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Dedicated to my wife
who has been
supporting me throughout

PREFACE TO SEVENTH EDITION

The sixth edition of the book was well received by pharmaceutical industry, pharmacy educational institutions and regulatory agencies. International scenario has changed so far as GMP is concerned with the publications of ICH, ICH Q8, ICH Q9 and ICH Q10 in particular. WHO took note of this and revised its GMP text. The major change is incorporation of principles of quality risk management (QRM). WHO has also published guidelines on QRM. This and other changes prompted me to review and revise the sixth edition of this book. A chapter has been included on QRM.

Research and development (R&D) is an important activity in pharmaceutical industry. Principles of quality by design (QbD) in pharmaceutical development will lead to better quality of drugs. The recommendations made in the ICH Q8 have already been accepted by the participating countries i.e. U.S., Europe and Japan. A brief discussion on ICH Q8 has been included in this edition.

Medicinal gases have important role in health care. Medicinal gases are regulated under the Drugs & Cosmetics Rules. There are no supplementary GMP guidelines on medicinal gases in India. EU GMP guidelines have supplementary guidelines on medicinal gases. Similarly, Health Canada and US FDA have guidance documents. Considering the need of medicinal gases manufacturers, a chapter has been included on GMPs for medicinal gases.

The entire text of sixth edition of the book has been reviewed and updated and some contents have been dropped as they related to small section of readers.

This revision would not have been possible without feedback from the readers, friends and critics. I thank the readers and critics who have gone through the sixth edition of this book and conveyed their views. I expect their views on the seventh edition also.

I am thankful to Mr. Satish Agrawal of Grato Enterprises for his help in composing the text. My thanks to Niti Dauneria for designing the cover of the book. I thank the printers, M/s. Rakmo Press Pvt. Ltd. who have been printing all the books authored by me. I express my gratitude to all the persons who directly or indirectly have helped me in reviewing this book. I look forward for similar support in future also from all my wellwishers and friends.

June 2015 P.P. Sharma

PREFACE TO FIRST EDITION

It is now well understood that final testing of a finished product alone is not sufficient to ensure the quality of drug. The developed countries realized this much before and prepared guidelines to be practiced during manufacture of a drug. These guidelines were given the name. Good Manufacturing Practices(GMPs).Today, many developing countries have evolved their own GMPs. In India, GMPs were given a statutory status as late as June, 1988 and have been included in the Drug and Cosmetics Rules, 1945. My personal experience while inspecting pharmaceutical manufacturing units revealed that the technical staff in a majority of these units did not have adequate training in GMPs. In the GMPs, under the Drugs and Cosmetics Rules, a note at the beginning reads as "To achieve the objectives listed below, each licensee shall evolve methodology and procedures which should be documented and kept for reference and inspection." Without proper training in GMPs the technical staff specially in the small scale sector feel at a loss as to how to go about it. I had an opportunity to undergo training in GMPs jointly organized by Danish International Development Agency and WHO in Nov. 1987 at Bombay. I have therefore, made an attempt to bring out this book wherein I have tried to offer guiding principles and practical guidelines to help the industry in formulating the methodology and procedures during manufacturing of drugs. Various formats have been designed for documentation which, I am sure, will help them to prepare various records required to be maintained under the rules.

Many drug manufacturers are, now, exporting drugs to developing countries. Majority of these importing countries, if not all, demand a free sale certificate under the WHO Certification Scheme. The certificate stipulates that the product has been placed in the market for sale in the country of origin, and the plant in which the product is produced is subject to inspections at suitable intervals and conforms to requirements of good practices in the manufacture and quality control of drugs as recommended by the WHO. Therefore, a text of WHO GMPs and Certification Scheme has been included in the text of the book.

In the second and third chapter, text of GMPs under the Drugs and Drugs and Cosmetics Rules and GMPs as laid down by

WHO have been reproduced. Chapter four and five deal with the practice of GMPs. Some aspects., though very important for practice of GMPs, have not been included either in GMPs under Drugs &. Cosmetics Rules or WHO GMPs. These have been included in the sixth chapter. For the guidance of the industry, additional precautions that should be taken during manufacture of large volume parenterals have also been included in this chapter.

This is my first venture. Undoubtedly, it will have scope for improvement. I would welcome suggestions from any quarter so that subsequent edition becomes more useful. In bringing out this book, I have kept in mind the needs of small scale Pharmaceutical Industry. I hope it is found useful by the technical persons responsible for building quality of a drug during its manufacture.

I am grateful to Dr. D.B. Anantha Narayana of Dabur Research Foundation and Mr. S. Yellor of Albert David Ltd. for going through the text of the book and for making valuable suggestions. I am thankful to WHO for permitting me to reproduce the text of WHO GMPs and certification Scheme. I am also thankful to Shri Mohan C. Bazaz for guiding me in the publication of the book.

September 1991 P.P. Sharma

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INTRODUCTION

If one goes through history of drug legislations of various countries, he finds that drug legislations were enacted essentially to stop distribution of deteriorated or adulterated drugs which, at that time, were mainly crude drugs. One of the oldest drug legislation is drug legislation of the United States of America. In 1848, US Congress approved a law to stop import of deteriorated and adulterated drugs. After over half a century, in 1906 the first pure food and drug law was approved under the Federal Food and Drug Act. This Act recognized the National Formulary (NF) and the United States Pharmacopoeia (USP) as the official standards for drugs listed in these compendia. The drugs official in these compendia were required to meet the standards set out therein. Most of the drug legislations followed this approach. But this approach could not prevent tragedies and mishaps caused by drugs in many countries. Simple things like mix ups of labels among other reasons were identified to be the causes of mishaps. It was realized that testing of final product alone was not sufficient to rely upon quality, safety and efficacy of drugs. Various amendments were made to the Federal Food and Drug Act since 1938, but it was only in 1962 (Kefauver Harris Amendments) that a drug was defined as "adulterated" if the methods used in its manufacture/processing, testing, packaging or storing did not conform to the good manufacturing practices (GMPs). As a result of this definition, the first GMPs were published in June, 1963. Thus very concept of GMPs was born in America. The major contribution of this amendment was introduction of preventive approach to control the quality of drug products. These regulations were first revised in January, 1971. A major revision appeared in late 1978. The current regulations, GMPs appear in part 210 and part 211 of Title 21 of Code of Federal Regulations (CFR) published by the Food and Drug Administration, Department of Health & Human Services of USA (see Appendix I).

In nineteen hundred sixties, the question of assessment of quality of drugs in international commerce was discussed many a time in the World Health Assembly (WHA) in view of the concern voiced by various countries regarding prevalence of substandard drugs in international trade. As a result of these discussions in WHA, resolutions were passed requesting member states to control

the quality of drugs for export in the same manner as was being done for drugs for domestic market. But it was felt that there was need for some international norms. WHO requested an expert committee to draft GMP. The committee prepared the draft. The first draft of WHO GMPs appeared as an annex to twenty-second report of WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968. This text of GMPs was revised along with the revision of WHO Certification Scheme and was made an integral part of it. Since then the text of GMPs has been revised a couple of times. At present, the main principles of WHO GMP appear in the WHO Technical Report Series 961. Several supplementary GMPs have appeared in different WHO Technical Report Series (*see* Chapter 2 of this book).

In the United Kingdom, Medicines Inspectorate of Department of Health and Social Security in consultation with other interested bodies compiled. 'Guide to Good Pharmaceutical Manufacturing Practice' in the year 1971. The Guide, popularly referred as 'Orange Guide', deals with those aspects of quality, safety and efficacy which may be affected by manufacturing processes. This guide has been revised a couple of times. However, the Guide has no statutory force, it is recommendatory in nature.

Either with the help of WHO guidelines or of their own, by the end of seventies, many countries had their own texts of GMPs. Later on, European Countries (EU) decided to have common GMP for EU countries. With time these GMPs have been revised a couple of times.

Though the concept of GMPs was known in India but it was brought under the legislation in June, 1988 only under Schedule M to the Drugs & Cosmetics Rules, 1945. The Schedule M was revised in 2001 (*see* Appendix II).

In recent times, the scope of quality control has extended much beyond laboratory. An examination of pharmaceutical operations will reveal that errors may occur anywhere from receipt of raw materials to final product. Lin, Lachman and Senkowski* have classified sources of quality variations into four major sources.

Sources of Quality Variations

1. Materials
   (a) Variation between supplier of the same substance
   (b) Variation between batches from the same supplier

*The Theory and Practice of Industrial Pharmacy, L. Lachman, H. Liberman,]. Kanig, Lea and Febigar, Philadelphia. 1976. p. 701.

(c) Variation within a batch

2. Machines
   (a) Variation of equipment for same process
   (b) Difference in adjustment of equipment
   (c) Ageing and improper care
3. Methods
   (a) Inexact procedures
   (b) Inadequate procedures
   (c) Negligence by chance
4. Men
   (a) Improper working conditions
   (b) Inadequate training and understanding
   (c) Lack of interest and emotional upheavals
   (d) Dishonesty, fatigue and carelessness.

Sources of quality variations are required to be controlled, if the quality of the product is to be assured and consistency is to be achieved.

Another important development has been appearance of the guidelines of the International Organization for Standardization (ISO), particularly, ISO 9000 to 9004, standards for quality management system. With the development of these concepts, various national and international texts of GMPs have been revised e.g. Guide to Good Pharmaceutical Manufacturing Practice (orange Guide), 1983 has been superseded by Good Manufacturing Practice for Medicinal Products in the European Community. The text of WHO GMPs was revised and was published as an annex to the Thirty-Second Report of WHO Expert Committee on Specifications for Pharmaceutical Preparations. First two parts of WHO GMP were supplemented with some more guidelines. The revised text of these two parts appears as Annex 4 to Thirty-seventh Report of WHO Expert Committee on Specification of Pharmaceutical Preparations (WHO Technical Report Series 908). This text has been revised and now appears as Annex 3 to WHO Technical Report Series 961.

Generally texts of GMPs provide guidelines on important aspects of manufacture of drugs like premises, personnel, equipment, sanitation, starting materials, manufacturing operations, validation, quality control systems, documentation etc.

One would ask, what are the objects of GMPs? The following are the main objects of GMPs;

- to produce product(s) conforming to the predetermined specifications;

- to produce product(s) of consistent quality;
- to minimize contamination;
- to eliminate error(s).

Many Indian drug manufacturers are exporting pharmaceutical preparations to developing countries which are participants to WHO Certification Scheme. These countries require a certificate from regulatory agency that the product to be exported has been placed on the market in the country of origin and that the plant in which it has been manufactured is subjected to inspection at regular intervals and the plant conforms to requirements for good practices in the manufacture and quality control of drugs as recommended by WHO. Therefore, Indian drug manufacturers as well as their technical personnel should be aware of the GMPs prepared by WHO. For convenience, these GMPs have been referred to as the WHO GMPs. WHO GMP and the Certification Scheme has been discussed in Chapter two of this book.

As mentioned above, GMP were introduced under Schedule M for the first time in June 1988. National Human Rights Commission (NHRC) while disposing of a matter relating to quality of large volume parenterals (LVP) recommended review of GMP and bring it to the level of international texts. In view of this, Government of India has reviewed the Schedule M. The revised Schedule M was notified by the Government of India, Ministry of Health and Family Welfare in December 2001 (G.S.R. 894(E) dated 11th December, 2001). It has been brought to the level of WHO GMP text. Provisions of revised Schedule M were to be made effective with effect from January, 2004 in case of already existing manufacturing units. In view of the representations made by several small scale pharmaceutical manufacturers associations, applicability of amended provisions was extended by one year. Subsequently a further extension of six months was given. The revised Schedule M has become effective from 1st July, 2005. However, the revised provisions were made applicable from the date of notification in case of units established after December 2001. Revised Schedule M has been reproduced as Appendix II to this book for the benefit of readers.

Manufacture of biological products is carried out employing biological processes which have some special features. Therefore, supplementary guidelines for biological products have been given in Chapter 5 and are based on WHO supplementary guidelines for biological products.

Some products which may either be conventional products or biological products but have some unique features and therefore,

require specific guidelines. Supplementary guidelines for quality assurance of some such products have been given in Chapter 6 of this book. The products covered in this chapter include recombinant DNA (rDNA) products and large volume parenterals (LVP).

Because of availability of a large number of patients in different regions in India and low cost of clinical trials, many contract research organizations (CRO) have come up in India and are carrying out clinical research. Many more may come up in future. Both WHO and European Union (EU) have texts of GMP for investigational pharmaceutical products. Several CRO may be working for companies which may have operations in those countries. In view of this, a chapter was added in the 6th edition of this book on GMP for investigational products and has been retained.

In India, GMP for homoeopathic medicines were notified by the Ministry of Health and Family Welfare, Government of India on October, 2006 and were made effective from November 2008. There are a number of homoeopathic medicine manufacturers in India. Many operations in homoeopathic medicine manufacture are similar to manufacture of modern medicine. As such, GMP principles are equally applicable to both. In view of this, a chapter was included in the 6th edition of this book on GMP for homoeopathic medicines and has been retained in this edition.

New trends are emerging in the quality assurance of pharmaceutical preparations. For example, Process Analytical Technology (PAT). US FDA has prepared guidelines on PAT and it is inviting industry to implement PAT on voluntary basis. At present, it is not a part of the regulation. Similarly, WHO has prepared a write up on hazard and risk analysis in pharmaceutical products which is based on hazard analysis and critical control point (HACCP). HACCP has been considered to be a food safety management system. The concept of HACCP is being applied to other industries. It can well be applied to the pharmaceutical industry. These concepts have been included in the book.

International Conference on Harmonization (ICH) has drafted ICH Q8 – Pharmaceutical Development, ICH Q9 – Quality Risk Management, and ICH Q10 – Pharmaceutical Quality System. Quality Risk Management (QRM) now appears in the texts of GMPs of ICH participating countries and WHO GMP. Therefore, a chapter on QRM has been added in this edition of the book. These documents were sent to participating countries for incorporation of principles elicited in the documents. Participating countries have incorporated these concepts in their GMPs. Both the students of

pharmacy as well as technical staff of pharmaceutical industry, particularly those whose companies are exporting must know the principles laid down under ICH Q9 and ICH Q10. The corrective action and preventive action (CAPA) system appears under ICH Q10 and also under ISO:9001. Realizing its importance it has also been covered in Chapter 10 of this book besides ICH Q8 and ICH Q10.

Since many of the excipients are not manufactured as drugs in India, GMPs are not enforceable on the manufacturers. There are no separate GMPs for excipients in India. In view of this, chapter 4 which related to GMPs for excipients has been deleted from this edition.

The book has been mainly patronized by pharmaceutical industry and pharmacy educational institutions and not by hospitals. Therefore, regulatory provisions of GMPs for blood banks have been deleted from chapter 6 of this edition.

Chapter 1

INDIAN GMPs

Quality, efficacy and safety of drugs has always been a matter of concern for public. Drugs being a very important component of health care system need special attention in regard to their quality, efficacy and safety. A brief review of over half a century of drug scenario in India will show us how we have come a long way in controlling the quality of drugs.

Over half a century from now India was a colonial country. Majority part of the country was under British rule. A small part was under Portuguese (i.e. Goa, Daman and Diu). A significant population of Europeans were living in India because of their occupation in army, civil and judicial services. This necessitated import of medicines into the country from Europe, mainly from U.K. Prof. Harkishan Singh[1], in his book History of Pharmacy in India and Related Aspects, Volume 3 has given a vivid account of British period pharmacies which included European establishments, chemists in United Provinces, pharmacies in Punjab and Delhi, druggists at Quetta and Karachi, Indian concerns and small time drug dealers. Some notable European establishments were:

Calcutta	Smith, Stanistreet & Co.
(Now known as Kolkata)	Bathgate & Co.
	R. Scott Thomson & Co. Ltd.
	Frank Ross & Co. Ltd.
Bombay	Kemp & Co. Ltd.
(Now known as Mumbai)	
Bombay & Poona	Treacher & Co. Ltd.
	Phillips & Co. Ltd.
	Thomson & Tayler
Lucknow	Murray & Co.
	Peake, Allen & Co.
Simla	Symes & Co.
	E. Plomer & Co.
	William Cotton & Co.
Delhi	Bliss & Cotton
	Kemp & Co.
	E. Plomer & Co.

Some notable Indian concerns were:

Calcutta	B.K. Paul & Co.
(Now known as Kolkata)	M. Bhattacharya & Co.
Bombay	S. Brothers
(Now known as Mumbai)	I.G. Gajjar & Co.
	Bill & Co.
	Popular Pharmacy
Madras	Dadha & Co.
(Now known as Chennai)	Appah & Co.
	Wilfred Pereira Ltd.
Delhi	H.C. Sen & Co.
	Young Friends & Co.
	Dr. Sahib Singh & Sons
Lahore	Beliram & Brothers
	Narayan Das Bhagwan Das & Co.
	Dr. Jai Singh Taran Singh & Sons

Apart from these notable pharmacies, there were hundreds of small time drug dealers. At that time, there were no drug or pharmacy laws in India. As such, any one could open a chemist shop and sell drugs. There was a large trade in patent medicines mainly imported into the country. Since there was no regulation on quality and distribution of drugs, prevalence of substandard and untested drugs was a menace. Therefore, it was brought to the notice of the Council of State by the Medical Professionals of that time. As a result of this, a resolution was moved in the Council in March 1927. The Council, in resolution, recommended to the Governor General to request all provincial governments to take such steps as may be possible to control indiscriminate use of medicinal drugs and to legislate for the standardization of the preparations and for sale of such drugs. But the resolution remained a piece of paper only. Frustrated with this, leaders of medical profession spearheaded the movement to boycott British drugs. The movement was slow initially, but gained momentum later on and spread throughout the country. The Government appointed the Drug Enquiry Committee in 1930 to counteract the agitation of the leaders of the medical profession. The Committee concluded that drugs and medicines whether imported or manufactured in the country were subjected to considerable adulteration and that in order to secure effective uniformity, central legislation was required for setting up of suitable standards.

When the Government did not react to the recommendations of the Drug Enquiry Committee for a long time, the Council of State passed a resolution in September, 1935. The Council

recommended to the Governor General to initiate early measures to implement the recommendations of the Drug Enquiry Committee and if for financial or other reasons he has to delay giving effect to the recommendations of the Committee, to take early steps to pass legislation which would effectively prevent sale of spurious drugs. The Government took two years to examine and deliberate and ultimately an Import of Drugs Bill was introduced in the Legislative Assembly in August, 1937. Since the Bill was limited only to the Import of Drugs, it was referred to the Select Committee in October. 1937.

Report of the Select Committee was presented in the Legislative Assembly on 15th March, 1940 and was later discussed. The historic Bill was passed in the Assembly on 5th April 1940. Then it was discussed in the Council of State and ultimately was passed on 10th April, 1940.[2] This legislation gave powers to the Government to make rules to regulate import, manufacture, sale and distribution of drugs.

Rules under the Drug Act were framed in 1945. To give effect to these rules, provincial governments were required to issue notification. These notifications were issued by the provincial governments over a couple of years.

The standards to which imported drugs or drugs manufactured in the country should conform were prescribed under the Act. We did not have our own pharmacopoeia. Drugs official in pharmacopoeia of other countries were required to comply with the standards laid down therein. In 1946, the Government of India published a Pharmacopoeial list which served as a supplement to the British Pharmacopoeia. After publication of this list, the Government appointed the Indian Pharmacopoeia Committee in 1948 to prepare a National Pharmacopoeia. The first edition of Indian Pharmacopoeia was complied by the Committee and subsequently published in 1955. Thus, the drugs and drug formulations official in the Indian Pharmacopoeia were required to comply with test for quality, strength and purity laid down therein.

Later, scope of the Drugs Act was extended to the cosmetics in 1962 by Drugs (Amendment) Act, 1962 and the title of the Act was changed to the Drugs & Cosmetics Act. Ayurvedic (including Siddha) and Unani drugs were also brought within the purview of the Drugs & Cosmetics Act by the Drug & Cosmetics (Amendment) Act. 1964. The second schedule to the Act in which standards for drugs imported into or manufactured in India for sale or distribution are set out was amended in March 1966 and standards for

homeopathic medicines were prescribed. As the situation warranted there have been more amendments in the Act and Rules made thereunder. After a review, in brief, of drug legislation in India, let us look at growth of pharmaceutical industry in the country.

In early twentieth century, drug manufacturing concerns could be counted on tips. Some notable names are Bengal Chemical & Pharmaceutical Works, Smith, Stanistreet & Co., Wilfred Pereira Ltd., H.C. Sen & Co. It is only after independence that pharmaceutical industry started developing. In the three decades (between the sixties and nineties) the pharmaceutical industry has grown phenomenally as may be seen from the figures given below:

Year	*No. of Pharmaceutical units*[3]
1969-70	2,257
1979-80	5,156
1989-90	16,000
1998-99	20,053

Today, we are manufacturing a number of bulk drugs and several thousand finished products. We have not only become self-sufficient in pharmaceutical formulations, but are exporting pharmaceutical formulations. According to one survey the Indian pharmaceutical market rose from 5.12 billion USD in 2002-03 to 8.16 billion USD in 2006-07. The market is expected to scale upto 15 billion USD by 2011-12.[4] Similarly exports grew from 2.9 billion USD in 2002-03 to 6.15 billion USD in 2006-07. Such a phenomenal growth demands an effective regulation.

Our quality control systems were designed on the concept that if a formulation conformed to the prescribed standards, it should be taken as a product of quality, efficacy and safety. But this concept did not hold good as evidenced by various drug mishaps in several countries out of unintended contamination or adulteration and the concept of GMPs emerged in nineteen hundred sixties in United States of America. But, not many people became aware of the concept in the sixties. WHO played a significant role in making manufacturers of drug formulations and national governments aware of GMPs through its certification scheme and India was no exception. But except for multinational companies and a few companies in organized sector, GMPs did not find favour with a large number of small and medium scale pharmaceutical companies. This scenario called for a regulation which would make GMPs obligatory for manufacturers of drug formulations. In view of the above and to

fall in line with other nations, the Government of India amended the Drugs & Cosmetics Rules, 1945 vide G.S.R 735(E) dated 24th June 1988 and prescribed GMPs under schedule M to the rules.

Schedule M as notified in June 1988 has two parts, Part I and Part II. GMP guidelines have been laid down under Part I. Part II contains requirements of plant, machinery and space for different categories.[5] Over the years, there have been changes in the GMP texts globally. GMP texts of European countries have been superseded by common text, known as EU GMP Guide. WHO has also revised its GMP text a couple of times. For more details on WHO GMP text, see Chapter 2. In a case of large volume parenteral, The National Human Rights Commission (NHRC) recommended review of GMP by the Government of India.

In view of the foregoing background, the Government of India has revised Schedule M. The Schedule M was revised by Notification No. GSR 894 (E) dated 11th December, 2001. For the prospective drug manufacturing units the requirements of Schedule M have become applicable with the date of notification while for the existing drug manufacturing units, these requirements were to take effect from 1.1.2003, but this date was extended a couple of times. Finally, the revised Schedule M became applicable with effect from 1.7.2005. Minor changes were made to the Schedule M by notification No. GSR 431(E) dated 30.6.2005.

The elements and sub-elements of the revised Schedule M are:[6]

1. General Requirements
   - 1.1. Location and Surroundings
   - 1.2. Building and Premises
   - 1.3. Water System
   - 1.4. Disposal of Waste
2. Warehousing Area
3. Production Area
4. Ancillary Areas
5. Quality Control Area
6. Personnel
7. Health, Clothing and Sanitation of Workers
8. Manufacturing Operation and Controls
9. Sanitation in Manufacturing Premises
10. Raw Materials
11. Equipment
12. Documentation and Records

13. Labels and Other Printed Materials
14. Quality Assurance
15. Self-Inspection and Quality Audit
16 Quality Control System
17. Specification
18. Master Formula Records
19. Packaging Records
20. Batch Packaging Records
21. Batch Processing Records
22. Standard Operating Procedures (SOPs) and Records, regarding
23. Reference Samples
24. Reprocessing and Recoveries
25. Distribution Records
26. Validation and Process Validation
27. Product Recall
28. Complaints and Adverse Reactions
29. Site Master File
    - 29.1 General Information
    - 29.2 Personnel
    - 29.3 Premises
    - 29.4 Equipment
    - 29.5 Sanitation
    - 29.6 Documentation
    - 29.7 Production
    - 29.8 Quality Control
    - 29.9 Loan Licence Manufacture and Licensee
    - 29.10 Distribution, Complaints and Product Recall
    - 29.11 Self-inspection
    - 29.12 Export of Drugs

Part IA lays down specific requirements for manufacture of sterile products, parenteral preparations (small volume injectable and large volume parenterals) and sterile ophthalmic preparations. These requirements include the following:

1. General
2. Building and Civil Works
3. Air Handling System (Central Air-conditioning)
4. Environment Monitoring
5. Garments
6. Sanitation
7. Equipment
8. Water and Steam Systems
9. Manufacturing Process

10. Form-Fill-Seal (FFS) Technology or Blow-Fill-Seal (BFS) Technology
11. Product Containers and Closures
12. Documentation

Part IB lays down specific requirements for manufacture of oral solid dosage forms (Tablets and Capsules). These include:

1. General
2. Sifting, Mixing and Granulation
3. Compression (Tablets)
4. Coating (Tablets)
5. Filling of Hard Gelatin Capsules
6. Printing (Tablets and Capsules)
7. Packaging (Strip and Blister)

Part IC lays down specific requirements for manufacture of oral liquids (Syrups, Elixirs, Emulsions and Suspensions). These include:

1. Building and Equipment
2. Purified Water
3. Manufacturing

Part ID lays down specific requirements for manufacture of topical products i.e. external preparations (Creams, ointments, pastes, emulsions, lotions, solutions, dusting powders and identical products).

Part IE lays down specific requirements for manufacture of metered dose inhalers (MDI). These include:

1. General
2. Building and Civil Works
3. Environmental Conditions
4. Garments
5. Sanitation
6. Equipment
7. Manufacture
8. Documentation

Part IF lays down specific requirements of premises, plant and materials for manufacture of active pharmaceutical ingredients (bulk drugs). These include:

1. Building and Civil Works
2. Sterile Products
3. Utilities/Services
4. Equipment Design, Size and Location
5. In-process Controls
6. Product Containers and Closures

Pre-revised Schedule M had 16 elements only and there

were no specific requirements for different dosage forms and active pharmaceutical ingredients (bulk drugs).

Part II of Schedule M lays down requirements of plant, equipment and minimum space for different categories of drugs. Categories in the Schedule include the following:

- external preparations
- oral liquid preparations
- tablets
- capsules
- surgical dressing
- ophthalmic preparations
- pessaries and suppositories
- inhalers and vitrallae
- repacking of drugs and pharmaceutical chemicals
- parenteral preparations

As stated earlier, the revised Schedule M has been modified at few places by notification vide G.S.R. 431 (E) dt. 30.6.2005. For the convenience of readers, revised Schedule M has been reproduced in Appendix II. A detailed discussion on the elements of GMP will be discussed in the Chapter 3. Readers may refer to Appendix II for detailed requirements in respect of plant, equipment and space of different categories.

As mentioned in this chapter, the Schedule M to the Drugs & Cosmetics Rules have been revised and has been brought, more or less, to the level of WHO GMP text. Discussion on various elements of GMP, Indian and WHO has been dealt in Chapter 3. Those elements which are common to both Indian and WHO GMPs have been discussed first. Later on those elements which are not common have been discussed.

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