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Review Article

Good Manufacturing Practice (GMP): History, structure and its significance

Abhimanyu Rampal*, S P Yamini Kanti

Dept. of Applied Chemistry, Amity University Noida Sector-126, Uttar Pradesh, India 201301

Abstract

Good Manufacturing Practice (GMP) is set of guidelines enforced by USFDA under 21 CFR. Every Manufacturer of Food, Cosmetics, Pharmaceuticals products, Medical Devices & Dietary products should follow these guidelines in order to be sure that their product is safe and effective to be put in the market and for use by general population. The parameters of GMP for different Categories may vary but there is only one aim & that is to prevent any kind of harm that can occur to the final user of the product.

Keywords: GMP, USFDA, EUROPE, CANADA, TGA, ANVISA

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*Corresponding author Tel.: +91-9953402923;
E-mail address: abhimanyurampal5@gmail.com (Abhimanyu Rampal).

1. Introduction

There were many tragic events happened around the world with respect to the safety & efficacy of drugs which lead to the deaths of many people. After all these incidents FDA felt the urgent need to propose some guidelines in order to ensure that the product coming to the market and to the users should be regulated by GMP. (1)

Some of the events which led to Birth of Good's Manufacturing Practices are as Mentioned below –

- **Case study of 1901**- there were children suffering from Diphtheria & they were given an antitoxin for their treatment which was prepared from Horse Serum. All of the children who received that treatment died cause of Tetanus as the serum was infected with Tetanus and case the led to the Biologics Control Act which was introduced in 1902. According to this act, it regulates the safety & purity of Vaccines, Sera's & Biological products. (2)
- **Case Study of 1937** – another tragedy happened during this year, which killed almost 107 children. An elixir formulation of Sulfanilamide was formulated to be used by Children for Gonorrhea & strap throat. But later, after the deaths of many children, they discovered that liquid formulation contains a poison which is was the same chemical which is used as antifreeze and this case led to the formation of Federal Food, Drug & Cosmetics Act of 1938 & after that, the companies for the very first time were required to prove the safety of their products to FDA, before marketing them directly. (3)
- **Case Study of 1941** – A Company introduced Sulfathiazole tablets which were contaminated by Phenobarbital, a Sedative and with the consumption of this tablet nearly 300 people were killed, & with such large no. of deaths, it persuaded FDA to make revisions in their guidelines for Quality Assurance/Control & Manufacturing. (4)
- **Case Study of Thalidomide, 1957** – It was introduced in West Germany, Europe as over the counter drug for Anxiety, Morning Sickness & Trouble in Sleeping. When the Regulatory Authorities gave Permission to sell this Drug for the said symptoms, they didn't have any idea about its side effects.
- After sometime, pregnant women started consuming this drug for their associated Symptoms which further resulted in their babies were born with deformed pair of limbs & after this incident the congress realized that this drug was Teratogenic & it was removed from the Market. (5)
- After all these incidents, the government came to realize that the quality & safety testing done at the end point is not enough and the same check should be done at each step so that the product meets all its standards.

2. Sections of GMP

Before Initiating any procedure, it is required that it should be properly defined and the necessary requirements & facilities are provided. Only trained personnel should be allowed in practice, approved procedures should be used, Availability of storage & transport facilities & proper records should be maintained and usage of correct materials, suitable equipment & premises is encouraged. (6)

Pharmaceuticals GMP in India is known as Schedule M, a part of Drug & Cosmetics Act, 1940. Schedule M is required to be followed by manufacturers operating Pharmaceutical Manufacturing Units. Schedule M comprises of 2 parts. (7)

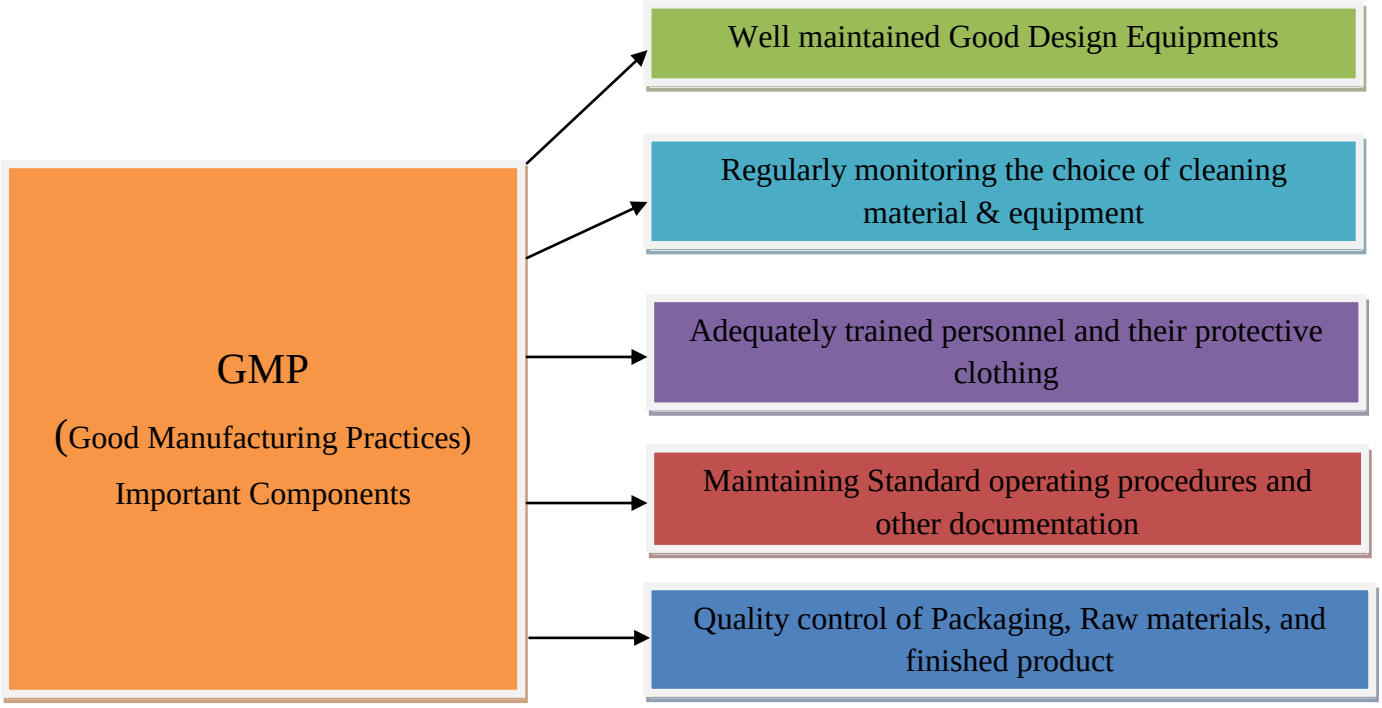

Figure 1. Important components of GMP

Part 1 – GMP for Premises & Materials

It further includes:

- General Requirements
- Production area
- Ancillary area
- Personnel
- Warehouse
- Quality Control Area
- Manufacturing operations & Controls
- Health, Clothing & Sanitation of workers
- Raw Material
- Equipment
- Labels & other Printed Materials
- Documentation & Records
- Sanitation in the Manufacturing premises
- Self-inspection & internal quality audit
- Quality control system
- Specifications
- Master Formula Record
- Batch Processing Record
- Packaging Record
- SOPs
- Reference Sample
- Reprocessing & Recovery
- Validation & Process Validation
- Product Recall
- Distribution Record
- Market complaints & Adverse Reaction

Site Master file

Part 1A- Requirements for Manufacturing of Parenteral & Ophthalmic Preparations

Part 1B- Requirement for Manufacturing of Oral Solid Dosage Form (Tablets & Capsules)

Part1C- Specific Requirements for Manufacturing of Oral Liquids

Part1D- Specific Requirements for Manufacture of External Preparations

Part 2 – Requirement for Plant & Equipment (7)

3. General Requirements (7)

The Building & Premises which is to be used for the manufacturing, processing, packaging, warehousing, testing & labeling should be –

- Provided with adequate space to work & to orderly arrange all the materials & equipment & should also allow movement of personnel.
- Compatible with the other operations that can be carried out in the same area.
- Avoid all chances of mix-ups between different drugs, raw materials, intermediates, contamination & cross contamination.
- The premises should be constructed in a way to prevent insects, pests, rodents & birds entry. The

walls of the rooms should be smooth & free from cracks and should allow easy painting and disinfection.

- The premises should be well Air-Conditioned in all the areas where it is required, properly lighted, ventilated & should have air handling units to maintain temperature, humidity inside the building.
- Proper drainage system should be there in building, open channels shall be avoided & timely cleaning & disinfection should be done.
- The walls & floors of the manufacturing unit should be free from the cracks & open joints to avoid accumulation of dust. The walls should be smooth so that they can be properly cleaned periodically.
- All the cleaning and painting records of the building should be maintained regularly.

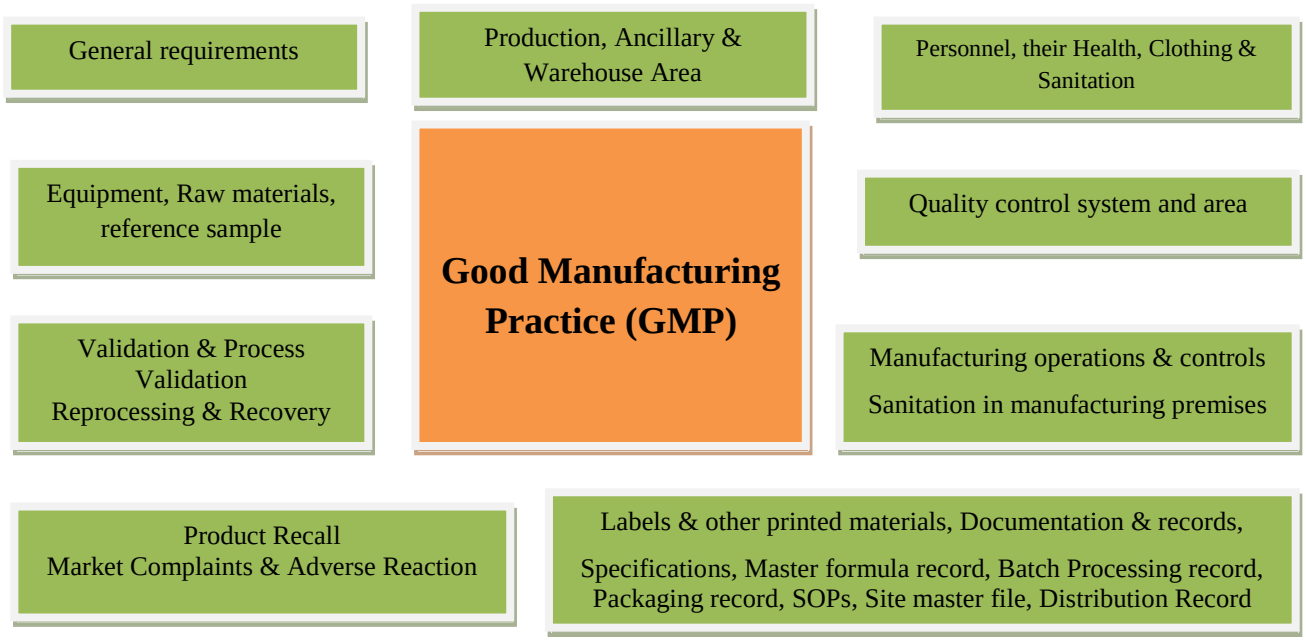

Figure 2. Combined components of GMP

Water System *(7)*

Availability water treatment system must be there so as to get purified water to carry out all the operations except washing and cleaning. The water shall be stored in tanks and these tanks should be cleaned periodically to ensure that water is free from any microbial growth, & records should be maintained.

Disposal of waste *(7)*

The Disposal of waste from the premises should be in accordance with the requirement of Environment Pollution Control Board. All Bio-medical waste shall be destroyed as per biomedical waste Rules, 1996.

There should be proper rules & provisions for the safe storage of waste materials awaiting disposal.

Hazardous, flammable & toxic substance should be stored in suitably designed areas.

All the records should be maintained time to time.

Warehouse Area *(7)*

Warehouse area should be designed in such a way that they shall be clear, dry & maintained. Temperature should be maintained at all times, the area should remain free from rodents, pests, & well equipped with proper bins & platforms.

There should be a separate warehouse area for raw materials and excipient and the area must be designed so that there is sufficient place for different materials & products for starting & packaging materials, API & finished products, intermediates, products in quarantine, products released, rejected, recalled & returned spare parts of machines & equipment.

Narcotics, Psychotropic drugs & substance should be stored in safe & secure areas to avoid any hazardous situation.

Sampling & storage of sterile materials should be done in Aseptic area.

The area should be regularly checked for any kind of leakage or breakage of containers.

All the records should be maintained from time to time.

Ancillary Areas *(7)*

There should be separate rooms for Refreshment, Rest, Changing, Storing clothes & washing for personnel's. Toilets should be separate for males & females.

These Ancillary areas should be separate from other areas & shall not lead directly to the manufacturing units.

Periodically cleaning and disinfecting records should be maintained.

Quality Control Area *(7)*

These areas should be designed to avoid any kind of mix-ups & cross contamination, there should be proper space for test samples, reference standard, reagents & records.

Separate area for Physico-chemical, biological, microbiological analysis. Periodically cleaning should be done. Airlocks & Laminar air flow should be there in microbiology section.

Personnel *(7)*

All the manufacturing procedures & testing of products should be performed under the supervision of competent technical staff, which has the required qualification and experience in the same.

Staff for Quality Assurance & Quality Control section should be qualified & experienced in the same. All the duties for the technical staff & personnel responsible for QA/QC shall be laid & followed by them strictly. Adequate no. of personnel's should be employed with proportion to the workload in the premises

Sanitation & Health *(7)*

All the personnel should undergo medical examination for full body; they should be free from any diseases like skin, communicable or contagious, tuberculosis, before employment.

A physician must be appointed for the health checkup of all the personnel or assessing their health status.

Staff handling the Beta-Lactum antibiotics should be tested for Penicillin sensitivity, & those handling cytotoxic substance, potent drugs & sex hormones should be examined by physician periodically for any kind of adverse effects, & these personnel should be employed in these sections on rotation to safeguard their health.

All personnel should be trained well for personal hygiene & should be well observed if they are following all the instructions or not. Smoking, Drinking, keeping food, medicines & drinks should not be allowed in the production, storage, laboratory & other areas.

All staff should report about their illness to their supervisor, if they have any.

All the premises shall be cleaned & maintained periodically to ensure that they are free from waste, dust etc.

There should be proper space for working & in-storage space to avoid mix-ups & contamination.

Materials, Equipments, Packaging materials

As per the starting materials specification shared by QC, to the purchasing department, they order materials to be used for the production purpose.

They usually make orders with a supplier who is approved by QA, QC & production department.

All the material that is received from the suppliers should be stored separately from each other & after checking all the materials, each one is labeled as quarantine with code no., material name, lot no. & date received. (8)

All the labels for quarantine, released & rejected should be in different colors so as to avoid any kind of errors. All the equipment used for production should conform the specified quality parameters. (9)

They should be designed in a way so that it's easy to clean up. The material of the equipment should be well polished, smooth, no difficult corners, uneven joints, to avoid contamination & difficulty in cleaning. The material of the equipment should be non-reactive in nature with the products so as to avoid any reaction or contamination. Packaging material which comes in direct contact with product should be of high grade quality so that it does not cause any contamination. (10)

Validation *(9)*

Validation is an important part of GMP and it should be performed as per the protocols. All the results & conclusions of validation process should be recorded, documented & maintained.

All the processes & procedures that had gone under validation should be revalidated time to time to ensure that they can give the desired results.

All the buildings & premises design should comply with the specifications of Design & they should operate in accordance to their design specification.

Self-Inspection & Quality Audits *(7)*

A team should be made by the management including staffs who are experts in their respective fields. These teams can perform self-inspection in the production & Quality control area time in a timely manner or on special occasions to make sure that the manufacturer is carrying out all the procedures in accordance with GMP.

These self-inspection or quality audits can help in detecting any shortcoming in GMP implementation & corrective measures can be taken within time.

The procedure of self-inspection should be well documented including results, conclusions, evaluation & the corrective actions.

There should be proper written instructions for –

1) Premises with personnel facilities
2) Personnel
3) Storage facility for raw material & finished products
4) Documentation
5) Quality control
6) Sanitation & Hygiene
7) Complaints
8) Validation & Re-validation program
9) Procedures for recall

Complaints & Product Recalls *(7)*

All the complaints related to the quality of the product must be very carefully reviewed & recorded &

there should be a written procedure for carrying out this process.

If any serious adverse event occurs from the use of any drug, it should be recorded & documented with the concerned authority.

A well-structured SOP should be drafted in the premises for recall of the products.

All the product recalls should be documented and the necessary corrective actions are to be performed timely.

Documentation *(11)*

For GMP & Quality Assurance, Documentation of each and every process or procedure is an important part. Quality Management system defines all the types of Documentation required.

Through Documentation we can regulate all the procedures which are related to medicinal products.

Common types of documents which are used in industries are as mentioned below-

- **SOP (Standard Operating Procedures)** –this is a document in which step by step instruction of all process and procedures are mentioned.
- **Test Method-** it provides step by step instruction for testing materials, products, task, supplies etc.
- **Policies** – all the aspects of GMP o be complied by the Manufacturer in the premises.
- **Site Master File** – it includes all the information related to the Manufacturing site.
- **Quality Handbook** – it includes all the rules & regulations which are to be followed by the company.
- **Batch Record** – it includes step by step instruction for the entire task related to production area & these records are basically maintained by manufacturing unit.
- **Batch Processing Records** – its documentation of each processed batch of the product & it complies with the approved master formula.

  1) Before processing every new batch, it should be verified that the instrument & the working station is properly clean & clear of previous products & suitable for use.
  2) While processing every new batch, following information should be recorded by a designated person employed for the operations –
     a) Product name
     b) Number of the batch which is being manufactured.
     c) Operator's name or the person responsible for checking the process at each step.
     d) Date & time of starting of any procedure, intermediate stage & completion of process.
     e) Information about any material, equipment or event used.
     f) Batch no. of the starting material
     g) Amount of product yielded at different stages of procedure
     h) Record of all the in-process controls, results yielded & the name of person who carried out all of them.
     i) Record all the deviations occurred in the procedure from the master formula.

- **Batch Packaging Record** (12) - It should be in accordance with the packaging instructions and it should be maintained for every batch.

  Before packaging each batch, it is made sure that the working station & the equipment is clear of the waste of previous the batch products

4. GMP Certification Process: INDIA (13)

1) **Application** – it's the first step of GMP Certification. It includes basic information of the company. The application needs to be accepted by the certification body.
2) **Review of application** – after receiving the application, it should be reviewed by a team to make sure it complies with the entire requirement.
3) **Quote & Agreement** – After reviewing the application, the quote is provided to the clients & gap analysis is carried out so as to cover all the clauses & quality standard sections.
4) **Documentation Review** - Checking of documents to make sure they comply with the requirements.
5) **Stage 1 Audit** –
6) **Review** – Checking the documents, procedures of your company in comparison to the compliance requirement.
7) **Corrective Action** – Take proper corrective action in case of non-conformity.
8) **Verification** – Documents should be verified according to the required standards.
9) **Stage 2 Audit** –During this second audit, the auditor checks whether the company is following rules & regulation according to its documentation and if they have identified any non-compliance, then the auditor gives an opportunity to the company to correct the particular non-compliance.
10) **Review** – Reviewing of the implementation of regulation according to the documents of company.
11) **Corrective Action**- if they identify any non-conformity, then corrective action has to be taken.

12) **Verification** – verify that all the rules & regulations are being followed by all the employees.

13) **Granting of Certification** – after checking all the parameters for compliance, the certification body issues a certificate of compliance, valid for 3 years.

14) **Surveillance Audit** – After the certificate is issued, once in every 6 months period, a surveillance audit should be performed to ensure that the company fulfills all the requirements of management system.

15) **Re-Certification** –it's done after every 3 years.

- **Review** – review that the company complies with the requirement of the management system.
- **Corrective Action**- if they identify any non-conformity, then corrective action has to be taken.
- **Verification** – compare all the company's documentation with the compliance requirement.

Table 1. Worldwide Agencies Regulating GMP

S. No.	Countries with Regulatory Agencies	Product to be inspected
1.	Canada – Health Canada	API's and Finished products (14)
2.	Australia (Therapeutic Goods Administration	API's and Finished products (15)
3.	Brazil (National Agency for Sanitary Surveillance, ANVISA)	Finished Pharmaceuticals (16)
4.	United States	Bulk Pharmaceutical Chemicals (17)
5.	Europe	API's & Finished Formulation (18)
6.	United Kingdom(Medicine and Healthcare Products Regulatory Agency, MHRA)	Finished Pharmaceuticals (19)
7.	South Africa (Medicines Control Council)	Finished Pharmaceuticals (20)

Table 2. GMP Guidance Documents Websites

S.No.	Country/Agency	Website
1.	Europe	https://ec.europa.eu/health/documents/eudralex/vol-4_en (21)
2.	United States	https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations (22)
3.	International Conference of Harmonization	https://www.ema.europa.eu/en/ich-q7-good-manufacturing-practice-active-pharmaceutical-ingredients (23)
4.	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)	https://picscheme.org/en/activites-gmdp-harmonisation (24)
5.	Canada	https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001/document.html (25)

5. Conclusion

GMP is a practice for production & testing of medicinal products in order to assure that the general population gets medicinal products of excellent quality. There have been different guidelines all over the world for regulating the quality of medicinal products but all of them have the same goal of safeguarding the health of patients as well as manufacturing good quality medicinal products.

Excellent quality can be achieved by properly planning & implying of Quality Assurance system and complying with GMP guidelines.

GMP can be effectively implemented only if we have knowledge about all the components of GMP starting from the Premises till the product development step.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Learoyd.P. Good Manufacturing Practices or 'GMP' A Brief Guide, NBS-Scientific and Technical Training STT-040; 2005 Sept.
2. Shadle. PJ. Overview of GMPs, BioPharm International [Internet]. 2004 [cited 2020 Aug 12]. Available from: http://www.biopharminternational.com/biopharm/artile/articleDetail.jsp?id=134225&pageID=2.
3. FDA. An Overview of FDA [Internet]. US:FDA; 2007 [cited 2020 Aug 17]. Available from:

http://www.fda.gov/ oc/opacom/fda101/sld013.html
4. Time Line: Chronology of Drug Regulation in the United States [Internet]. US:FDA; 2007 [cited 2020 Aug 27]. Available from: http://www.fda.gov/cder/about/history/time1.html
5. Immel. BK. A Brief History of the GMPs, Regulatory Compliance Newsletter. Winter [Internet]. GMP Labeling; 2020 [cited 2020 Aug 17]. Available from: http://www.gmplabeling.com/catalog/news1105.pdf
6. WHO TRS. WHO expert committee on specifications for pharmaceutical preparations: thirty-second report. Geneva :WHO technical report series- 823, ISBN 92 4140823 6, ISSN; 1992 .p. 0512- 3054.
7. Schedule M. good manufacturing practices and requirements of premises, plant and equipment for pharmaceutical products; [Internet]. New Delhi: CDSCO; 2012 Mar 25 [cited 2020 Aug 17]. Available from: cdsco.nic.in/html/GMP/Schedule(GMP).pdf
8. PIC/S Secretariat (Ed.): Guide to Good Manufacturing Practice for medicinal products, Pharmaceutical inspection convention/ pharmaceutical inspection co-operation scheme PE 009-2 1 July 2005. Geneva: PICS; 2004 Jul
9. US food & Drug Administration. CFR code of federal regulation [Internet]. USA: FDA; 2019 Sep [cited 2020 Aug 12]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211
10. Huber. L. Validation of analytical methods and procedures. [Internet]. Lab compliance; 2012 Mar 25 [cited 2020 Aug 17]. Available from: labcompliance.com/tutorial/methods/default.aspx.
11. Eudralex: 2012. Eudralex-Volume 4 Good manufacturing practice (GMP) Guidelines [Internet]. EU: EMEA; 2011 Jan [cited 2020 Aug 17]. Available from: ec.europa.eu/health/documents/Eudralex/vol-4/index_en.htm.
12. WHO TRS: Annex 2 Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In; WHO expert committee on specifications for pharmaceutical preparations. Geneva: Fortieth report WHO technical report series 937; 2006 .p. 45-84.
13. Absolute Quality Certification Pvt. Ltd. GMP Certification, [Internet]. 2020 [cited 2020 Aug 13]. Available from: http://www.absolutecertification.com/GMP.aspx [Accessed on 2 November 2020].
14. Government of Canada. Health Canada [Internet]. Canada: Health Canada [Internet]. 2020 [cited 2020 Aug 13]. Available from: https://www.canada.ca/en/health-canada.html
15. Australian Government. Therapeutic Good's Administration [Internet]. Australia: TGA; 2020 [cited 2020 Aug 12]. Available from: https://www.tga.gov.au/.
16. Ministerio da saude. Agencia National de Vigilancia Sanitaria [Internet]. Brazil: ANVISA; 2020 [cited 2020 Aug 12]. Available from: https://www.gov.br/anvisa/pt-br.
17. US Department of Health & Human Services. US food & Drug Administration [Internet]. US: USFDA; 2020 [cited 2020 Aug 12]. Available from: https://www.fda.gov/home
18. European Union. European Medicines Agency [Internet]. EU: EMA; 2020 [cited 2020 Aug 12]. Available from: https://www.ema.europa.eu/en
19. UK Government. Medicines & Healthcare products Regulatory Agency [Internet]. UK:MHRA;2020 [cited 2020 Aug 12]. Available from: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
20. South Africa Government. South African Health Products Regulatory Authority [Internet]. SAHPRA; 2020 [cited 2020 Aug 12]. Available from: https://www.sahpra.org.za/
21. European Commission. Medicinal Products. Eudralex-Volume 4. GMP Guidelines [Internet]. EU: EMA; 2020 [cited 2020 Aug 16]. Available from: https://ec.europa.eu/health/documents/eudralex/vol-4_en
22. USFDA. Current Good Manufacturing Practice Regulations. Code of Federal Regulations. [Internet]. US:USFDA;2020 [cited 2020 Aug 16]. Available from: https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations
23. European Medicines Agency. ICH Q7, GMP for Active Pharmaceutical Ingredient [Internet]. EU: EMA;2020 [cited 2020 Aug 16]. Available from: https://www.ema.europa.eu/en/ich-q7-good-manufacturing-practice-active-pharmaceutical-ingredients
24. PIC/S. GM (D) P Harmonization. GMP Standards [Internet]. PICS; 2020 [cited 2020 Aug 16]. Available from: https://picscheme.org/en/activites-gmdp-harmonisation
25. Government of Canada. Health Canada. Good Manufacturing Practices guide for drug products [Internet]. Canada: Health Canada; 2020 [cited 2020 Aug 16]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001/document.html