GMP and regulations

3

3.1 Introduction

The pharmaceutical industry is highly regulated by the application of the principles of good manufacturing practice (GMP). In most countries, government agencies provide guidance to pharmaceutical manufacturers that is intended to facilitate the manufacture of safe, unadulterated and efficacious drug products. The pharmaceutical industry is one of the most highly regulated, and regulation is enforced by governmental and international agencies [1].

The sterile pharmaceutical sector has a well-defined set of expectations and regulations that provide clear statements relating to microbiological controls and monitoring. In contrast, the expectations for nonsterile pharmaceuticals are poorly defined, with few specifics written in either legislation or guidance publications. The regulatory agencies, therefore, expect the industry to take a risk-based approach to microbiological control and apply appropriately justified monitoring in the manufacture of nonsterile pharmaceuticals [2]. This chapter outlines the key requirements for GMP that can be applied across the pharmaceutical industry.

With microbiological aspects of GMP, top level microbial oversight "governance" should be driven by senior level site management and not limited to the senior microbiologist or quality assurance (QA) manager. Clear direction needs to be given to the site emphasizing that microbiological contamination control is a key factor in GMP. Multifunctional involvement of representatives from manufacturing (technical and operations), engineering, QA management, and quality control (QC) microbiology should have a collective responsibility to ensure the appropriate quality systems are in place to ensure microbiological control.

3.2 Good manufacturing practice

GMP refers to the rules governing the manufacture of a safe and efficacious pharmaceutical product. There are two main global bodies that oversee GMP. These are the US Food and Drug Administration (FDA), where manufacturers are governed by the Code of Federal Regulations (CFRs), in particular 21 CFR 210–211, and the European Union (EU GMP), which is overseen by the European Medicines Agency (EMA). To complement this, the World Health Organization (WHO) has a GMP system, although this, to an extent, draws upon EU GMP [3]. There are, additionally, national GMP systems operative in most countries. Here there are invariably different nuances that add an extra dimension to the regulatory process [4].

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The different regulatory agencies control the production of medicines through various licences, such as:

- manufacturers licence;
- manufacturers specials licence;
- marketing authorization licence;
- wholesale dealers licence;
- investigational medicinal products (IMPs) licence.

Compliance with these licences is assessed routinely through GMP inspections, which are normally conducted every 2 years (although with "risk-based" inspections this frequency can alter). Regulators aim to assess whether the pharmaceutical company is manufacturing the product in the way that is stated in licences, policies, procedures, and other official documentation.

Not all aspects of GMP are written down in regulations, such as innovations relating to the latest technologies. This part of GMP is called "current" or cGMP. It is up to each pharmaceutical organization to be familiar with the current "hot topics." Connected with GMP is good distribution practice (GDP), focused on the distribution of medicines; good clinical practice (GCP), which is concerned with clinical trials; and good laboratory practice (GLP), where the focus is animal experimentation. GLP should not be confused with GCLP (good control laboratory practice). GCLP, which covers QC, is a subset of GMP. Collectively, these different aspects of best practice are commonly abbreviated to GxP [5].

The two dominant sets of GMP guidance are those that relate to the EU (operated by the EMA and national agencies) and the US CFR, which form the basis of inspections by the FDA.

3.2.1 EU good manufacturing practice

The principles and guidelines of GMP are set out in two EU Directives: 2003/94/EC covers human-use medicines and 91/412/EC veterinary-use medicines. The texts of these Directives are included and expanded on in the EU GMP guide, which is contained in Chapter 4 of EudraLex on the European Commission. This guide covers GMP for medicinal products and also for starting materials used as active ingredients [6].

3.2.2 FDA and CFRs

The FDA's legal authority to regulate both medical devices and electronic radiation-emitting products is the Federal Food Drug & Cosmetic Act (FD&C Act). The FD&C Act contains provisions, that is, regulatory requirements, which define the FDA's level of control over these products. The CFR is a codification of the general and permanent rules that are published by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation.

Most of the FDA's medical device and radiation-emitting product regulations are in Title 21 CFR Parts 800–1299. These final regulations codified in the CFR cover various aspects of design, clinical evaluation, manufacturing, packaging, labeling, and postmarket surveillance of medical devices.

3.2.3 Key aspects of GMP compliance

There are many important parts of GMP compliance. GMP has five main attributes:

- safety,
- identity,
- strength,
- purity,
- quality.

Of these, the most critical are [7]:

- Proper documentation and records—"if it is not recorded it never happened" according to the inspectors. It is important that all actions, events, and decisions relating to the quality of the product must be recorded at the appropriate level of detail in a controlled way;
- Control of materials. This refers to ensuring that all materials used, whether they be the raw materials, components such as bottles or stoppers, and packaging materials, are of the sufficient quality and are traceable;
- Thorough housekeeping and cleaning. GMP requires that people work in an orderly and methodical way and that work areas are neat, tidy and, there is segregation between tasks where required. This will reduce the potential for errors and mix-ups to occur;
- Responsible personnel behavior. This includes such areas as reporting incidents and errors immediately, and behaving appropriately in controlled areas (such as minimizing particles and microbial contamination in cleanrooms);
- Process control at all steps. This level of control relates to ensuring that all parameters are in control throughout the manufacturing process (e.g., time, temperature, pH) and reporting immediately if there is a noticeable drift or adverse trend;
- Maintenance of equipment. This involves ensuring all equipment used in the manufacture of product is "fit for purpose" and is cleaned, maintained, calibrated, and verified as appropriate and labeled/recorded as such. This is supported through initial and on-going validation. Any equipment not fit for purpose should ideally be removed or clearly labeled [8].

3.2.4 Ten rules of GMP

The essential elements of GMP can be conveyed to personnel in a way that is easy to understand as a useful training aid. GMP requires that initial and on-going training must be provided for all personnel whose duties take them into production areas or into controlled laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

Ten suitable GMP "rules," to be used for staff training or to act as a reminder, are set out below.

1. Confirm you are trained and have correct written instructions before starting any job?
2. Follow instructions exactly.
3. Report errors and bad practices immediately.
4. Ensure you have the right materials before you start a job.
5. Use the correct equipment for the job, confirm its status and cleanliness.
6. Maintain good segregation. Protect against contamination.
7. Work accurately, precisely, and methodically.
8. Maintain good standards of cleanliness and tidiness.
9. Ensure changes are pre-approved (through the change control system).
10. Do not make assumptions—check it out.

3.2.5 Risk management

An important part of GMP is risk management. On August 21, 2002, the FDA announced a significant new initiative: "Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century: A Risk-Based Approach." The objective was to enhance and modernize the regulation of pharmaceutical manufacturing and quality. The methodology was to use risk-based and science-based approaches for regulatory decision-making throughout the entire life cycle of a product. This initiative set forth a plan to enhance and modernize the FDA's regulations governing pharmaceutical manufacturing and product quality for human and veterinary drugs and human biological products [9].

The objectives were to:

- encourage the early adoption of new technological advances by the pharmaceutical industry;
- facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and QA;
- encourage implementation of risk-based approaches that focus both industry and FDA attention on critical areas;
- ensure that regulatory review, compliance, and inspection policies are based on state-of the-art pharmaceutical science;
- enhance the consistency and co-ordination of the FDA's drug quality regulator programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities.

The risk approach has been adopted by other regulators and reached international agreement through the documents issued by the International Conference on Harmonization (ICH), through the paradigm of "Quality Risk Management," namely ICH Q8—Pharmaceutical Development, ICH Q9—Quality Risk Management, and ICH Q10—Pharmaceutical Quality System.

3.3 Importance of medicines in public health

Medicines are a critical part of modern healthcare for humans and animals. A medicine is any substance or component that is administered for the purposes of diagnosis, treatment, cure, mitigation, or prevention of a disease. This definition can be extended

to include substances that modify physiological functions in healthy patients (such as preventing conception) and to other nondisease states (inducing anesthesia). The legal definitions of a medicine or a drug embody these concepts.

The terms medicinal substance, drug substance, and active pharmaceutical ingredient are used interchangeably by regulatory authorities and the pharmaceutical industry to describe the pharmacologically active component(s) of medicines, while medical product, drug product, and finished product are used to define the formulated drug substance that is administered to the patient or animal.

Hence, the way that medicines are controlled during development, manufacture, distribution, and use makes an important contribution to public health protection and also to ensuring that the public is neither exploited nor exposed to unacceptable risks from either prescribed or self-medication medicines. This level of control and assurance is achieved through GMP and regulation.

3.4 The role and development of pharmacopoeias

Pharmacopoeias have an important long-established role in the regulation of medicines. Their primary purpose is to set the standards for the active and inactive materials used in the preparation and manufacture of medicines. Thus, pharmacopoeial specifications and methods form the basis for the control of a large number of substances and materials used in the manufacture of medicines [10].

Pharmacopoeias were first developed at a national level and subsequently on a regional and an international basis. Examples of these three levels are the British Pharmacopoeia (BP), the European Pharmacopoeia (Ph. Eur.), and the International Pharmacopoeia (Ph. Int.). Other pharmacopoeias of importance in the international market for medicines are the US Pharmacopoeia (USP) and the Japanese Pharmacopoeia (JP).

These are similar documents, which in some cases present the same requirements and monographs albeit in a different language or format. However, it is important to understand that there are many differences between the requirements of pharmacopeias worldwide. Hence, microbiologists need to take care in including the correct pharmacopoeial requirements in regulatory submissions and in carrying out the correct tests for the market(s) where their products are authorized and sold. Unfortunately, this can lead to duplication of testing and different standards for the same attribute.

Pharmacopoeial standards are:

- objective, public standards of quality for medicines and their components;
- compliance requirements that provide the means for an independent judgement as to the overall quality of an article;
- requirements that apply throughout the shelf life of a medicinal product;
- used by a wide variety of organizations including suppliers, purchasers, manufacturers, inspectors, medicines regulators, and official and independent control laboratories.

Thus, a pharmacopoeia is an important legal component of the overall system for the control of medicines. It complements and assists the regulatory process by

providing what are effectively minimum or "default" requirements for the registration and control of medicines.

Pharmacopoeias contain monographs for chemical substances, antibiotics, and various biological substances. They also cover pharmaceutical dosage forms, general monographs, standards for materials and containers, general control methods, reagents, and reference standards used in testing. For microbiologists, there are many chapters of relevance including sterility testing, endotoxin analysis, tests for microbial limits, mycoplasmas, antibiotic assays, and so on. The USP is the most comprehensive of the available texts.

3.5 Importance of inspections in the lifecycle of medicines

The inspection of critical activities during the product lifecycle of medicines is an important means of ensuring compliance with the relevant legal requirements and guidance. Consequently, nations are required to have inspection and enforcement organizations. These agencies also require investigation and enforcement powers that include seizure of "violative" products and, in respect of the manufacture and distribution of medicines, injunctions, financial penalties and restrictions, and suspensions of legal authorizations.

3.5.1 Inspection process

Inspections are carried out against the requirements set out in the relevant regulatory submissions and authorizations (e.g., marketing authorization) and the relevant GxPs. They may be organized in different ways (e.g., part of the assessment of marketing authorization applications, review of quality systems, product or process flow, facility review, compliance with specific guidance).

The authorities will normally review relevant regulatory documents and the inspection history of an operation before it is inspected. In the case of manufacturing sites, this will normally involve the submission and review of a Site Master File giving an overview of the site, its layout, management organization, and systems. Inspections are normally announced beforehand; however, it should be noted that the authorities could, if required, carry out unannounced inspections at any time.

The inspection will proceed following an agreed program during which the organization being inspected should receive initial verbal feedback. Further feedback should be provided at the end of the inspection, and this should be confirmed in the inspection report, a copy of which is sent to the inspected organization.

The inspecting authority will subsequently ask for a response to the inspection findings. If the response is inadequate and the issues are serious, then formal enforcement action by the authorities can be expected.

Inspection is a recurring process with an expected frequency of around 2 years or more often if an organization has either product quality or compliance problems.

In the United States, the FDA applies a risk-based approach to inspections with particular emphasis on Quality Systems Inspection Technique (QSIT). The FDA focuses on cGMP requirements of 4–6 different systems (e.g., QC; although they always review the companies quality system).

3.6 Role of the company regulatory affairs department

Each pharmaceutical organization must have a regulatory affairs department. This department should have a full understanding of the requirements applying to the company's products and should also act as the repository for the information provided to the regulatory authorities in support of applications and changes to the company's marketing authorization. This should include the countries where the products are marketed, "local" regulatory requirements, and the up-to-date registration status.

The regulatory affairs department should also have information about the company's authorization(s), to manufacture, where appropriate to import and to distribute the company's products. Students are advised to ensure that they know how to obtain this information and how to stay up-to-date with regulatory requirements.

3.6.1 Pharmacovigilance

Pharmacovigilance is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. The legal framework for pharmacovigilance for medicinal products in the EU/European Economic Area (EEA) is set out in a number of Directives, which describe the obligations of marketing authorization holders and the regulatory authorities. This requires them to set up a system for pharmacovigilance in order to:

- collect, collate, and evaluate information about reported and suspected adverse reactions;
- share relevant information to allow all parties involved to meet their obligations and discharge their responsibilities.

Information about drug safety is obtained from a number of sources including:

- spontaneous adverse drug reaction (ADR) reporting schemes, for example, the UK's "Yellow Card" scheme;
- clinical studies and investigation of health and diseases in wider populations;
- information from pharmaceutical companies and information published in medical literature;
- information from regulatory authorities worldwide and from morbidity and mortality databases.

Marketing authorization holders are required to operate a system to monitor and report back to the authorities on the safety of their products. This requires the collection and reporting of spontaneous safety events, and the collection and evaluation of safety data from various sources over the life of a medicine. For new products, this is defined in a pharmacovigilance plan that is part of the risk planning information that accompanies an application for a marketing authorization.

3.7 Documentation

The pharmaceutical and allied industries have a requirement to document activities for a variety of reasons, but the main one is to ensure the quality, and, thus, the safety and efficacy, of the products they sell. The pharmaceutical industry, like a number of other industries, has legal requirements relating to documentation that are supported by guidance on how to meet the requirements of the legislation. The pharmaceutical industry has adopted the principles of ISO9000 in terms of several standards that are based on a combination of quality system management and GMP. These include ISO15378, "Primary Packaging Materials," ISO14385, "Medical Devices," and the PS standards for "Pharmaceutical Packaging Materials" and "Pharmaceutical Excipients." The FDA guidance for industry document, "Quality Systems Approach to Pharmaceutical cGMPs Regulations" has implicitly adopted these principles as well. Furthermore, in Europe, legal obligations on pharmaceutical manufacturers regarding documentation are defined in the "GMP Directive" 2003/94/EC.

The most important requirement in relation to documentation is with specific batch manufacturing documentation. The documents must make it possible to trace the history of each batch. This traceability needs to be possible for a minimum defined period (at least 1 year after expiry of the batch). Where electronic data are used, data must be protected against loss or damage. This means having a validated system of data recall should such a recall of data be needed.

A document can be a procedure or a record. Examples of a procedure could be the standard operating procedure (SOP) for conducting a sterility test or the routine testing of a purified water system. A record is often related to a specific SOP and carries the confirmatory details required of that SOP. The record of the sterility test SOP could be details of the product name, its batch number, and its test result.

When designing documentation, it is helpful to think of documentation as a process. The first stage can be described as event capture, but the information or event has no status unless it can be verified or approved, which is the second stage. The last part of the process is to communicate the event, which may be by circulating and implementing a document. To illustrate this, consider the Gram stain technique. To document the procedure we need to write down the steps that capture the process. As a part of a controlled system, the steps need to be verified as being correct and the procedure "signed off" (approval stage). The procedure can be issued in to routine use along with associated training, which is the communication stage.

GMP makes certain requirements of a documentation system such as:

- assigning responsibility to an individual for control of the system;
- ensuring layout, approval, authorization, and unique identification of all documents is provided for (often by a master "documentation SOP");
- having a master "documentation SOP" to include:
  - procedures for issue, retrieval, reissue, maintenance of currency, and traceability,
  - procedures for determining the need for documents,
  - identification of documents to be included in batch dossiers (for batch release),
  - linkage of documents to licences and regulatory requirements,
  - outlining audit requirements for the documentation system,

- ensuring that only the most up-to-date version is ever used,
- retention times and archiving.

Further considerations regarding the system controlling documentation suggests that:

- documents should be available at point of use;
- master copies, including electronic versions, are held under control;
- there is control over format;
- there is a slick system for changes, approval, and reissue;
- there is control of documents of an external origin.

The majority of these requirements also make up the elements of a "documentation lifecycle."

3.7.1 Types of documents

3.7.1.1 Specifications

Specifications tend to be documents that related to starting and packaging materials, as well as finished products. They describe the standards to which these materials and product must comply if they are to be approved for use or sale. Specifications are important for microbiological testing; for example, defining pass/fail criteria. A finished product specification should contain amongst others:

- the designated name of the product and the code reference where applicable;
- the formula or a reference to;
- a description of the pharmaceutical form and package details;
- directions for sampling and testing or a reference to procedures;
- the qualitative and quantitative requirements, with the acceptance limits, for example, the sterility test or absence of specified pathogens;
- the storage conditions and any special handling precautions, where applicable;
- the shelf-life.

3.7.1.2 Instructions

All instructions to personnel (e.g., media manufacture, bacterial identification, and so on) should be clear, precise, unambiguous, and written in numbered steps, in the imperative. They should be written in a language and style that the user can readily understand. Again, detail of the content can be found in Chapter 4, particularly Sections 4.14–4.16. Associated with instructions are records and these can be either combined with the instruction or a separate document. Content of batch manufacturing records (including media batches) can be found in Sections 4.17–4.18.

3.8 Conclusion

This chapter has covered the subjects of GMP, inspection, documentation, and regulatory affairs. The object was to provide some introductory information as to how the pharmaceutical sector operates. This chapter thus complements Chapter 2 in

providing the skeletal structure within which the pharmaceutical microbiologist must operate.

Of the elements covered, GMP is of overriding importance. GMP is the practices required in order to conform to guidelines recommended by agencies that control authorization and licensing for manufacture and sale of drug products, and active pharmaceutical products. These guidelines provide minimum requirements that a pharmaceutical product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public. As Chapter 1 emphasized, microbiological risks can be significant, and microbiological control is an important component of GMP.

References

[1] Walsh G. Biopharmaceuticals: biochemistry and biotechnology. 2nd ed. Chichester, UK: Wiley; 2003, p. 78.
[2] Baird RM, Bloomfield SF. Microbial quality assurance in cosmetics, toiletries and non-sterile pharmaceuticals. 2nd ed. Bristol, PA: Taylor & Francis; 1996, p. 51, 115.
[3] World Health Organization (WHO). Good manufacturing practices for pharmaceutical products. In: WHO Expert Committee on specifications for pharmaceutical preparations. Thirty-seventh report. Geneva: World Health Organization; 2003 [WHO Technical Report Series, No. 908, Annex 4].
[4] Grazal JG, Earl DS. EU and FDA GMP regulations: overview and comparison. Qual Assur J 1997;2:55–60.
[5] Verma K. Base of a research: good clinical practice in clinical trials. J Clin Trials 2013;3:128.
[6] EU GMP. EudraLex. Good manufacturing practice (GMP) guidelines, vol. 4. Brussels, Belgium: European Commission; 2014.
[7] Sandle T, Saghee MR. Compliance aspects of sterile manufacturing. In: Saghee MR, editor. Achieving quality and compliance excellence in pharmaceuticals: a master class GMP guide. New Delhi: Business Horizons; 2012. p. 517–60.
[8] Sandle T. Qualification and validation. In: Saghee MR, editor. Achieving quality and compliance excellence in pharmaceuticals: a master class GMP guide. New Delhi: Business Horizons; 2012. p. 169–206.
[9] Sandle T, Lamba SS. Effectively incorporating quality risk management into quality systems. In: Saghee MR, editor. Achieving quality and compliance excellence in pharmaceuticals: a master class GMP guide. New Delhi: Business Horizons; 2012. p. 89–128.
[10] Akers MJ. Sterile drug product: formulation, packaging, manufacturing and quality. New York: Informa Healthcare; 2010, p. 382.