MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Pharmaceutical Drug Regulatory Affairs Journal
ISSN: 2642-6315

Active Pharmaceutical Ingredients (API) Regulations in India, USA & Europe: A Comparative Study

Singh A, Sinha A and Ghosh M*

Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology Mesra, Ranchi, Jharkhand, India

***Corresponding author:** Manik Ghosh, Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology Mesra, Ranchi, Jharkhand, India, Email: manik@bitmesra.ac.in

Research Article

Volume 7 Issue 1

Received Date: October 10, 2023

Published Date: February 20, 2024

DOI: 10.23880/pdraj-16000153

Abstract

ICH Q7 i.e., Good Manufacturing Practice guide for Active Pharmaceutical Ingredients was the late outcome of ICH. The ICH Q7 Guideline is originally based on a PIC/S draft guideline on API and was adopted by PIC/S in 2001, then integrated as part II of the PIC/S GMP Guide in 2007.Q7 is a firm list of what makes an operating Pharmaceutical Quality System. Active Pharmaceutical ingredient is the crucial part of any drug product that can directly influence the safety and efficacy of the medicinal product which may endanger the life of the patient. For this, we have assessed the knowledge on regulatory guidelines adopted by three different counties and to observe API has an appropriate manufacturing process that country should follow the stringent rules under the country's respective regulatory barrier. We therefore looked onto the Main component of drug product i.e., 'API' taking into consideration the regulatory requirements associated with it in 3 different countries and the quality control parameters associated with same.

This study is the Elucidation of Regulatory Requirements of GMP i.e., the part of Quality Assurance for API in different countries and guidance for drug industry whose intention is to harmonize actions or processes within a specific discipline. During this study we strictly followed three different regulatory guidelines followed by USA (USFDA), INDIA (SCHEDULE M), EUROPE (EUROPEAN UNION VOL 4). It is imperative to manufacture API abiding by the standard guidelines for subsequent processing and formulation of high-quality raw material.

Keywords: Active Pharmaceutical Ingredient; Good Manufacturing Practice; Regulatory Guideline; Pharmaceutical Quality System; Quality Assurance

Introduction

"Any component or combination of substances intended to be employed in the manufacturing of a drug product and that, when employed in the production of a drug, forms an active ingredient in the drug product," according to ICH Q7. Such compounds are designed to provide pharmacological action or have influence in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to alter the body's function and structure. ICH Q7 provides guidance in respect to GMP's (Good Manufacturing Practice) in the manufacturing of API for intended use in human drug (medicinal) product. API process is a sequence of action which out turn in the formation of API [1]. Multi-step actions or steps may be included in an API procedure.

Chemical synthesis, Fermentation, Purification, Crystallization, Drying, Milling, Packing, Labeling and Testing

API manufacturers are anticipated to follow CGMPs throughout the API procedure, starting with the usage of starting materials and to confirm important procedure stages that affect the finished API's quality and purity. As the process approaches the final API, material quality conduct is intended to become more stringent. The level of control required varies substantially depending on the manufacturing process, and it increases as the process develops from initial intermediate stages to end separation and purifying phases. The danger of each process stage determines the effective control system [2].

Material and Method

1. This is a descriptive observational study; Data which was relevant to three countries regulations was mainly gathered from their government and official website which are-
2. US Food and Drug Administration, www.fda.gov
3. European Medicines Agency (Volume 4 EudraLex) ec.europa.eu
4. CDSCO (Central Drugs Standard Control Organization) cdsco.gov.in
5. The studies were also based on Title 21 CFR Part 210 - Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs. Title 21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals. www.ecfr.gov

Results

API	Regulatory	Requirement
USFDA	**EMA**	**SCHEDULE M (CDSCO)**
FOOD AND DRUG ADMINISTRATION COMPLIANCE PROGRAM GUIDANCE follows ICH Q7 i.e., GMP for API. It has long sighted that the CGMP required for the finished pharmaceutical is applicable in notion to Active Pharmaceutical Ingredients (API). FDA look forward to the API manufacturers to apply CGMP to the API processes and to validate the critical processes to yield a good quality and purity of the final API [1].	According to EU GMP‟s for API‟s - EU GMP Vol 4, Part II which is equivalent to the ICH Q7 / WHO guidelines the exporting country should have the written confirmation to meet the EU Manufacturing standard and to fulfil the prerequisites to ensure the protection for public health and for their intended use. Export will depend on the written confirmation issued by the 3rd Country local authority which is on the approves list of non-EU countries [2].	Schedule M of the "Drugs and Cosmetics Rules" contains Indian GMP criteria specified by Indian authorities. Unlike the ICH Q7, which only addresses APIs, Indian GMP laws do not differentiate between GMP for medicinal goods and GMP for APIs, with Part 1-F including API manufacture. Several adjustments to Schedule M have since been implemented, while others are still in the works [3].
These includes the proper facilitating building with a specific equipment along with the qualified personal and adequate written SOP to assure the proper and controlled manufacturing procedure ensuring stability of drug for the intended use.	In these guidelines Manufacturing involves all functioning of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control release, storage & distribution of API.	To provide a level playing field for Indian manufacturers, regulatory bodies are promoting the strategy of harmonizing Schedule M with the ICH/PICS. Along with the evaluation and modification of Schedule M, it is recommended that the Indian inspection agency's GMP inspection standards be reviewed and harmonized with worldwide standards in order to offer the Indian manufacturer the necessary boost on the global level.

Going through the guidelines we observed that apart from the regulatory applicability and quality risk management EMA follows the same standards as that of USFDA. But CDSCO (Schedule M) does not completely comply with the specifications as many parameters are not mentioned in the guidelines which we have briefly depicted below with the respective significance.

Quality Management

Individual processes and employees engaged in product manufacture are targeted by QMS, which stops them from

straying from quality standards like ISO and ICH Q10. It employs quality assurance ways of preventing quality deviations and emphasizes documentation to keep track of any issues and solutions. India should follow the specific meaning and significance of QMS in the guidelines [4].

Personnel

Under the personnel, in Schedule M it should be stated that all personnel should have their roles written down. The principal objective, role dimensions, outputs/responsibilities, reporting information, and essential competences should all be included in job descriptions or function descriptions. These should be checked on a frequent basis.

Pharmaceutical consultants help pharmaceutical businesses follow industry standards and provide medical treatments to patients quickly which indeed is needed by pharma industry to get guidance for consistent production of API with controlling and monitoring the production [5].

Buildings and Facilities

Depending on the route of administration of pharmacological medicines, different qualities of water are necessary. The European Medicines Evaluation Agency (EMEA) for advice on quality of water for pharmaceutical use (CPMP/QWP/158/01) is one source of information about different grades of water.

Indian regulators should specify about Containment as it refers to the technique of containing a chemical within a specific space, which is an effective method for safeguarding operators and the surroundings in the event of high toxicity and product reactivity. APIs (active pharmaceutical ingredients) are growing more potent, especially in new drugs. The market for high potency active pharmaceutical ingredients (HPAIs) e.g., cytotoxic compound is rising in double digits in several areas, fueled primarily by oncology medications [6].

Process Equipment

The quality of an API is inextricably linked to the cleaning technique used; as a result, producers must address this issue appropriately, and regulatory agencies must thoroughly examine this element during GMP inspections [7].

The use of computers to gather and compare data to produce an accurate study has greatly benefited the area of pharmacy. Computers' primary duty is to receive data, store it, process it, and disseminate it, and this continual flow of data demonstrates that any system is operating properly. So Indian regulation must include the part mentioning relevant to computerized system [8].

Documentation and Records

Schedule M guidelines should be included with the document's revision histories that are used to keep track of all the modifications made to it. This is a crucial feature since it allows you to simply trace down anyone who has misused your material. It also assures that a user can only see the current version of a document, and that only selected users have accessibility to prior versions.

The integrity of original documents and authentic copies must be preserved. True copies of original records (e.g., a scan of a paper record) can be kept in place if there is a documented system in place to verify and record the integrity of the copy. Any risk associated with the deletion of original records should be considered by companies [9].

If maintenance of equipment is required, it's critical to keep a detailed record - whether scheduled or unscheduled - to assist you comprehend how crucial it is to keep your equipment in good working order.

Materials Management

Materials management is essential for guaranteeing a steady supply of materials for production in order to meet customer needs. It not only guarantees that manufacturing schedules are met, but it also has the potential to lower end product prices while maintaining quality through the materials purchased and employed. The entire material management process involves the selection of raw material vendors and ends with the shipping of finished products to their final location [10].

Production and In-Process Controls

In a chemical manufacturing plant, in-process procedures are critical elements of quality control. For E.g., Temperature, light, heat, the surroundings, and the reaction vessel's surface must all be examined. As a result, every procedure must be examined and categorized individually in accordance with (ICH) Q7A guidelines. This activity is critical because a reaction step can produce a contaminant that can contaminate API, regardless of how far off the procedure is from the API [11].

Packaging and Identification Labeling of Apis and Intermediates

Packaging is an important aspect of the pharmaceutical industry's development of diverse drug formulations. The close connection between a pharmaceutical preparation and

its package, which is a major concern for medicine stability and safety, is a significant issue for pharmaceutical dosage form packaging. The packing material is selected for its efficacy and performance characteristics in protecting the quality, potency, and safety of the pharmaceutical goods. Containers, for example, are evaluated using a variety of methods, including crushed glass testing, whole container testing, chemical resistance testing, and water attack testing [12].

Storage and Distribution

"Any supplier of APIs, packaging materials, or services has the competence to consistently meet previously established requirements," APIC adds.

Independent quality units' roles within this framework should also be put down in the form of a contract or agreement. The committee also recommends the establishment of an independent quality unit to oversee quality assurance (QA) tasks such as documentation and traceability of API distribution activities.

Laboratory Controls

Quality control (QC) in the laboratory ensures that lab procedures and systems operate properly, and that accurate and reproducible results are obtained. In addition, the quality control processes developed in a laboratory serve as the foundation for the certification and accreditation process. It must be done on a regular basis, and quality control materials should be treated in the same manner as samples from beginning to end. From the examination of receipt of raw materials through dosage-form quality control, laboratory testing is required at practically every phase of pharmaceutical production and R&D. (QC).

Validation's major goal is to show that the analytical method is fit for the intended use and that it is accurate, specific, and precise over the analyte's given spectrum. Analytical Method Validation is required when modification is made to the technique, the composition of the medication product, or the manufacturing of the drug products [13,14].

Validations

The fact that validation is the most essential argument for validation is the regulatory necessity for virtually every operation in the global health care business for medicines, biologics, and medical devices. Reduced sample size and frequencies would seem to be easily rationalized if a process/product has been adequately validated, and hence deliver a measurable return on the validation effort.

It's a good idea to keep track of documentation of validation/qualification process. A broad declaration on validation policy, and also an explanation of the working process and the validation stage to be accomplished, must be included in the guideline. Handwriting the most vital information, such as test acceptance or rejection, as well as remarks on any deviations, is recommended [15,16].

Change Control

"Change control" is a vital component of any Quality Assurance programme. If a changes to a product component, process equipment, process environment (or location), technique of manufacturing or testing, or any other modification that could influence product quality or supporting system operation is suggested, written procedures must be established. For E.g., the manufacturer used a different granulation process for the sustained release tablet, the particle size and tablet fast releases are different, resulting in an uncontrolled rapid release of the active ingredient, putting the patient at risk of heart attacks.

Rejection and Re-Use of Materials

Materials and goods that have been rejected should be clearly labeled as such and kept in a secure area. Depending on the situation, they should be returned to the sellers, refurbished. Whatever steps are taken, authorized workers should approve and document it.

Reprocessing is the technique of reinstating non-conforming material into the previous phases of a verified manufacturing step to produce a product that fulfills all of the stated standards. To enhance product qualities or satisfy preset standards, it is bound to repeat a filtration or crystallization stage, and other relevant chemical or physical manipulation procedures. At a specific point of manufacturing, the insertion of all or part of earlier batches of the required quality (or re-distilled solvents and similar products) into a fresh batch is referred to as recovery. It encompasses both the elimination of contaminants from waste to achieve a product and the repurposing of previously used materials for new use [17].

Complaints and Recalls

Market complaints are major problems that might harm a company's inventory and reputation. Following the introduction of a product to the market, post-marketing surveillance will be carried out to track any negative effects on the population. The source of the complaint could be anything, such as transportation, manufacture, or packaging. As a result, market complaints are given increased priority.

Market complaints are addressed according to a set of procedures. If the complaint appears to be legitimate, a root cause study should be conducted to resolve the issue, and the products should be withdrawn from the market. The recall system should be effective enough to remove the product from the market in a timely manner [18].

Discussion

APIs are intended to be manufactured in accordance with GMP guidelines. Wherever the API-manufacturing or receiving countries is anticipated in compliance with adopted ICH agreements, API GMP is expected. The original ICH Q7A guideline was provided in November 2000 for acceptance by members of the International Conference on Harmonization, and the ICH named it Q7, with no substantial modifications. The members of the ICH (European Union, Japan, and the United States) officially adopted ICH Q7A, which was afterwards approved by many additional countries throughout the world, and even the WHO.

GMP deviations will almost likely occur without "inspections," and the frequency of these deviations will rise as the interval between "inspections" grows! Due to funding limits, personnel levels, as well as the realities of a much higher number of international companies selling into the United States, the FDA was unable to dramatically boost inspections. The FDA then unveiled its "Pharmaceutical CGMP for the 21st Century" effort in 2002, with end report issued in 2004, a programmer that recognized the FDA Commissioner's approach to pharmaceutical quality and inspections, which also comprise of a risk-based strategy. This strategy made better use of FDA resources and allowed business to apply technology more effectively. It would assist the FDA in prioritizing its GMP compliance activities.

Based on a review on the FDA website, the FDA granted a high number of General Warning Letters between 2010 and 2014.

Pharmaceutical Labeler/Relabelers Facilities

- Inability to keep detailed report of APIs
- Inability to provide your customers with any and all quality or regulatory data obtained from the API manufacturer
- Failure to keep track of repackaging, relabeling, and holding activities to avoid contamination and API integrity loss
- Lack of a Quality Unit in charge of examining and approving CGMP papers and procedures, as well as ensuring product quality
- There was a mislabeled container discovered. Consumers may be at risk as a result of the behaviors that led to this mislabeling occurrence.
- APIs are not kept up to date if they aren't kept up to date.

Laboratory Operations

- Failure to test APIs in the lab to confirm that they must fulfill specifications and produce results on Certificates of Analysis in a timely manner
- Inability to keep accurate records of all laboratory results
- Inability to guarantee that the equipment is sanitized and cleaned in a consistent and efficient basis
- Failed to guarantee API manufactured in accordance with established guidelines.
- The laboratory computer system lacking procedures to avoid information alteration, as well as audit trails (IT)
- Unauthorized access or alterations to data were not prevented.
- Employees were not given enough and training regarding documentation.

Inability to Keep Precise and Full Lab Test Data

- Failure to keep and make production and control records available for inspectional review
- Inadequate critical deviation investigations or a batch failure to meet standards

CGMP Violations Included

- Failure to create an efficient quality management system and to communicate to your customers the API manufacturer's quality or applicable standards.
- QU failed to verify batch production records prior to the delivery of an API batch.
- Failure to record production procedures as they are being carried out
- Failure to keep equipment in good working order

Since the FDA expanded its focus on API firms in specific countries, as indicated by an even more recent number of Warning Letters, the governments of API corporations are already under strain to solve the issues. This combination of internal and external regulatory pressure will either succeed, resulting in fewer GMP deviations, or it will fail, resulting in customer and public pressure as a result of recurrent discrepancies.

Conclusion

APIs have grown into a global sector from a US standpoint. APIs were locally sourced if available fifty years ago. This was especially true for pharmaceutical companies that conducted research. API production has grown outside of the United States as a result of the establishment of a vast

and rising generic business, as well as the global expansion of chemical and pharmaceutical industries. International sourcing concerns have become a source of increasing worry for the global pharmaceutical business. One of these issues was establishing an equitable regulatory competitive landscape that met GMP criteria.

Deviations from GMP can be avoided. Working to identify API GMP and establishing procedures and systems in place to meet it and having long - standing commitment from firm management and employees will go a long road ahead toward ensuring API GMP compliance.

References

1. (2016) Food and Drug Administration, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for industry. Silver Spring MD, USA, pp: 1-53.
2. (2014) Public Health European Commission. EudraLex-Volume 4-Good Manufacturing Practice (GMP) guidelines.
3. (2001) Schedule M-Part 1, Part 1 F, Schedule U, Schedule L1 to the Drugs and Cosmetics Act and Rules. New Delhi.
4. Priede J (2012) Implementation of quality management system ISO 9001 in the world and its strategic necessity. Procedia-Social and Behavioral Sciences 58: 1466-1475.
5. (2022) Indeed Career Guide. How to Get a Job as a Pharmaceutical Consultant.
6. (2022) Five essential criteria for increasing employee protection in the pharmaceutical industry-HET Filter.
7. Choudhary A (2022) Detergents Used for Cleaning of Pharmaceutical Equipment.
8. Bandameedi R (2016) Provenance of computers in Pharmacy. OMICS International.
9. (2022) Revision control in electronic document management system. Doc Control.
10. What is material management? (Definition, types and examples). TWI Digital Library.
11. Talley M, Zayas J, Sanchez V (2005) In-process control methods for the manufacture of APIs. Pharmaceutical Technology Europe 17(10).
12. Sabah A, Ahmed I, Arsalan A, Arif A (2014) Features, functions and selection of pharmaceutical packing materials.
13. (2020) Pharmaceutical lab testing: From API inspection to QA. News Medical net.
14. (2019) Laboratory quality control. Conduct Science.
15. (2022) Method validation of analytical procedures. Pharma Tutor.
16. (2022) Good practice guide: Process validation. ISPE.
17. (2020) Reprocessing and reworking-From confusion to clarity. API FIRST.
18. Kumar KA, Gupta NV (2015) Handling of Market Complaints and Recalls 7(3): 502-506.