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Review Article

Quality System Requirements of Dietary Supplements: An Overview of 21 CFR Part 111

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ABSTRACT

FDA has implemented 21 CFR 111 guidelines to regulate the production of dietary supplements that are sold in dosage forms. Creating an effective quality system demands both time and financial resources. However, the robust quality systems model of cGMP can offer the necessary controls to ensure acceptable quality. The current review focuses on the general quality system requirements of dietary supplements as per 21 CFR 111 regulations. The requirements mentioned in each subpart are discussed in the study. According to this study, a manufacturing firm can guarantee the consistency and quality of dietary supplements distributed to the USA by adhering to 21 CFR 111 regulations. A dietary supplement manufacturing company, therefore, has to comply with 21 CFR 111 and thus can be an FDA-approved plant. According to the findings of the study, a dietary supplement manufacturing firm can fulfill its commitment to quality by setting up a suitable quality system that can obtain the approval of the regulatory authorities to which it plans to export its products and thus can achieve customer satisfaction.

Keywords: Pharmaceutical Quality system, FDA, 21 CFR 111, SOPs, cGMP.

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INTRODUCTION

In the contemporary setting, quality has turned out to be a key element. Having quality implies meeting the defined standards while also taking into account the needs of the society we live in today, which is undergoing rapid change. In the pharma sector, quality cannot be compromised.[1,2] Regardless of the production method or company, customers expect the dietary supplements to be of the necessary quality to meet their expectations.[3] The Quality Management System (QMS) is used to oversee the quality of the dietary supplements manufactured in the herbal drug manufacturing industry.[4] To ensure product efficacy and subsequently product quality, the overall and final value of the product requires the input of safety, stability, etc., which are illustrated in Figure 1. Thus, maintaining a certain level of product quality (efficacy, stability and safety) necessitates an integrated set of procedures or practices. These include specific descriptions, agronomic or equivalent practices, harvesting techniques, holding procedures and manufacturing processes.[5]

Herbal medicines as dietary supplements have been used for thousands of years ago and are still in use now.[6] Humans have used natural products derived from natural sources like plants for food and medicines throughout history, notably plant parts or the entire plant to treat and prevent diseases.[7] There arevarious regional and national regulatory barriers questioning about the harmonization of herbal medicines regulations which is intricate and continually changing.[8]

In the United States, herbal medicines are not regulated as medicines. However, they are given special status as "dietary supplements," together with vitamins, minerals and other nutritional, as well as homeopathic and Ayurvedic medicines.[9-11] Dietary supplements are designed to enhance nutrition and food intake and have evolved beyond mere food adjuncts.[12] All domestic and foreign suppliers who produce, package and label dietary supplements for sale in the United States must comply with FDA regulations. This compliance is mandated by the Dietary Supplement Health and Education Act (DSHEA), enacted in 1994.[13]

The DSHEA fundamentally defined and regulated dietary supplements for the first time in the United States, enforcing precise FDA regulations and forbidding nutraceutical makers from making certain claims without supporting evidence.[14] Title 21 of the Code of Federal Regulations include the cGMP

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Figure 1: Quality management infrastructure.

regulations for each industry that the FDA regulates. There are specific variations in cGMP regulations for each category of supplements. Understanding how these changes will affect is essential, if the company sells a variety of products that fit into one or more of these major industry categories.[15] A high-level summary of the key GMP subjects demanded by the industry is presented in Figure 2.

On August 24, 2007, the FDA implemented 21 CFR 111, Current Good Manufacturing Practices (cGMP), for the manufacturing, packaging, labeling, or holding operations for dietary supplements.[16] This regulation, 21 CFR 111, parallels the drug regulation 21 CFR 211, which governs GMPs for pharmaceuticals. Although not approved as medicinal treatments, dietary supplements are utilized and marketed globally as alternatives to medication.[17,18] The FDA established Part 111 to regulate the production of dietary supplements, which are available in dosage forms such as tablets, capsules and liquids, similar to pharmaceutical products. Prior to 21 CFR Part 111, dietary supplements were regulated under Part 110, which pertained to food products. Companies manufacturing dietary supplements must adhere to Current Good Manufacturing Practices to ensure protocols are in place to verify the identity, potency, purity and composition of supplement ingredients.[19,20] The "c" in cGMP stands for "current," indicating that firms must continually update their adherence to GMPs in response to new scientific knowledge and industry best practices.There are six essential elements of cGMP which were illustrated in Figure 3.

Overview of 21 CFR 111 regulations

21 CFR 111 outlines the cGMP requirements for the manufacturing,labelling, package and storage of dietary supplements for humans. All domestic and international markets engaged in the production, testing, packaging, labeling and storage of dietary supplements, as well as those engaged in testing, quality control and distribution of dietary supplements in the United States, are required to adhere to the FDA regulations.[21] The Part 111 cGMP criteria is generally less strict and more flexible than the Part 211 cGMP requirements, even though they are equivalent.[22] The different subparts of 21 CFR 111 are mentioned in Figure 4.

Subpart A: General provisions

This section mainly highlights the applicability of the regulations. As per this section, the guideline applies to the current herbal drug manufacturing firm, since the firm focuses on manufacturing dietary supplements. As per this section, the regulation is not applicable if dietary supplements are meant for direct retail sales to specific customers. The section includes definitions of major terminologies related to the regulations.

Subpart B: Personnel

This section provides guidelines to prevent contamination that can occur through personnel as well as requirements for hygiene practices. Good hygiene practice is one of the important practices to prevent contamination as humans carry microorganisms that might contaminate the supplement and may affect the quality of the product. Excluding personnel with health conditions from working certain operations and using PPE kits are a few of the measures taken to prevent contamination. As per this section, it is necessary to have qualified personnel and supervisor. The guideline also mentions the requirement to provide training to the personnel based on their respective operations at the dietary supplements manufacturing firm. The firm can improve its quality system by implementing certain procedures for practicing hygienic procedures as well as providing proper training for personnel regarding the prevention of contamination.

Subpart C: Physical plant and grounds

The standards for sanitation, design and building of the physical plant and grounds are outlined in this section. The guidelines suggests requirements to maintain ground as well as physical plants. The guideline also mentions requirements for pest control as well as cleanliness maintenance of cleanliness. In addition, it alos provides the requirements for water supply, lighting and waste disposal. Maintaining cleanliness in and around physical plants and ground can be essential as it can reduce contamination of the supplements. Thus, quality can be maintained. So certain procedures must be implemented for cleaning the physical plants and grounds as well as pest control.

cGMPs	Food / Edible	Dietary Supplements	Pharmaceuticals	Cosmetics
Personnel	X	X	X	X
Facility and Grounds	X	X	X	X
Sanitary Operations	X		X	
Sanitary Facilities & Controls	X		X	
Equipment & Utensils	X	X	X	X
Process Controls	X	X	X	X
Warehouse & Distribution	X	X	X	
Human Food By-Products	X			
Defect Action levels	X			
Returned Products	X	X	X	
Complaints	X	X	X	X
Documentation, Records & Record Keeping	X	X	X	X
Packaging & Labeling	X		X	
Laboratory Controls			X	X
Raw Materials	X		X	X
Internal Audits				X
Control of Components			X	
Hazard Analysis, and Risk-Based Preventive Controls	X			

Figure 2: Summary of key FDA cGMP regulations across industry sectors.

Subpart D: Equipment and utensils

The equipment and utensils used in manufacturing facilities must be designed and constructed according to their specific requirements. The guideline mentions the requirement of SOPs for the operation, calibration and cleaning of the instruments and the requirements of qualification of instruments. The guideline depicts the requirements that are applied to automated equipment as well as the requirement to retain relevant records. The manufacturing firms must be compliant with FDA regulations regarding the SOPs for operating, calibrating and cleaning equipment and also for performing the qualification of instruments.

Subpart E: Requirement to Establish a Production and Process Control System

This section primarily outlines the requirements for achieving quality products. Establishing a production and process control system is crucial for ensuring product quality. According to the guidelines, the production and process control must be designed to ensure the product's quality. Additionally, proper quality

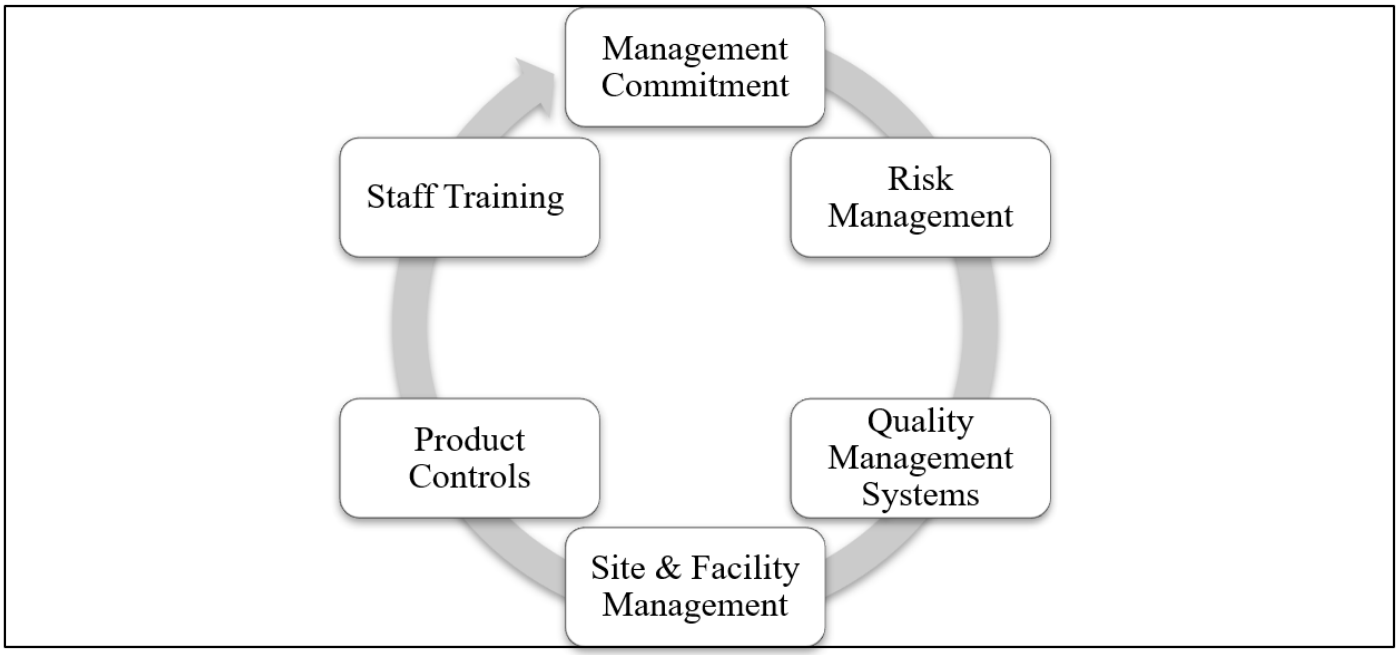

Figure 3: Six elements of cGMP.

SUBPART	SUBJECT OF SUBPART
A	General Provisions (including coverage and definitions)
B	Personnel
C	Physical Plant and Grounds
D	Equipment and Utensils
E	Requirements to Establish a Production and Process Control System
F	Production and Process Control System: Requirements for Quality Control
G	Production and Process Control System: Requirements for Components, Packaging, Labels and for Product that You Receive for Packaging or Labeling as a Dietary Supplement
H	Production and Process Control System: Requirements for the Master Manufacturing Record
I	Production and Process Control System: Requirements for the Batch Production Record
J	Production and Process Control System: Requirements for Laboratory Operations
K	Production and Process Control System: Requirements for Manufacturing Operations
L	Production and Process Control System: Requirements for Packaging and Labeling Operations
M	Holding and distributing
N	Returned Dietary Supplements
O	Product Complaints
P	Records and Recordkeeping

Figure 4: Subparts of 21 CFR 111.

control procedures must be in place to ensure that specifications are met.

Subpart F: Production and Process Control System: Requirements for Quality Control

Quality control operations are crucial for determining product quality and ensuring that only high-quality products are marketed. These operations involve reviewing materials and deciding to discard any that do not meet specifications. This section outlines the requirements for quality control personnel and their responsibilities. According to this section, raw and packing materials must undergo quality control checks before use. The guidelines also detail quality control requirements for handling returned products, product complaints and packaging

and labeling operations. Vendor qualification is also a key requirement to ensure quality.Subpart G: Production and Process Control System: Requirements for components, packaging and labels and for product that you receive for packaging or labeling as a dietary supplement

This section of the guideline encompasses the requirements about components, packaging and labeling as well as for the product that is supposed to be packed and labeled. As per this section, the quality of the components, packaging and labeling as well as for the product that is supposed to be packed and labeled must be in compliance with the FDA regulations.

Subpart H: Production and Process Control System: Requirements for the Master Manufacturing Record

This section establishes the requirements for the master manufacturing record and details to be included in the master manufacturing record. Manufacturing firms can comply with this part of dietary supplements cGMP by preparing the master manufacturing record according to these guidelines.

Subpart I: Production and Process Control System: Requirements for the Batch Production Record

This section establishes the requirements for batch manufacturing records and the information to be included in the batch manufacturing record. The firms can comply with this subpart of dietary supplements cGMP by preparing the batch production records in compliance with this subpart.

Subpart J: Production and Process Control System: Requirements for Laboratory Operations

This section encompasses the laboratory requirements. It highlights that laboratory processes must be established and followed. As per this section, the manufacturing firm should have adequate laboratory facilities and there must be appropriate laboratory testing methods. The firm should also have a proper record-keeping procedure for documents about. The manufacturing firms can comply with this subpart, if the requirements mentioned are met.

Subpart K: Production and Process Control System: Requirements for Manufacturing Operations

This section discusses requirements that must be met during manufacturing operations. It majorly deals with the prevention of contamination. As per this section, there must be the manufacturing operation that is selected or established must be such that it meets the requirements of the intended product as well as a proper procedure for handling rejected materials.

Subpart L: Production and Process Control System: Requirements for Packaging and Labeling Operations

This section encompasses the requirements that are applied to packaging and labeling operations. As per this section, the requirements for repackaging/ relabeling must be met. The manufacturing firm should also have procedures for handling rejected supplements for distribution.

Subpart M: Holding and Distributing

As per this section, the requirements for storing and distributing components, in-process products, packaging, labeling, finished product and reserve samples must be met by the firm to comply with this section.

Subpart N-Returned Dietary Supplements

This section addresses the requirements for handling the rejected dietary supplements. Unless quality control staff approve the salvage of the returned dietary supplement for redistribution or reprocessing, the returned dietary supplement must be destroyed or otherwise properly disposed of according to the cGMP regulations.

Subpart O-Product complaints

This section encompasses the requirements for product complaints. It encourages dietary supplements manufacturing companies to consistently look into customer concerns, regardless of whether they are about the effectiveness of a dietary supplement or the inherent safety of aproduct.

Subpart P-Records and recordkeeping

This section deals with the requirements of documents and retention of these documents. The records can also be stored as electronic records or as original and true copies. These documents must also be available during FDA inspection. The section also mentions photocopying or microfilming facilities.[23-25]

CONCLUSION

The quality of dietary supplements is assessed by ensuring that they meet specific quality system requirements. Implementing a proper quality system demonstrates a dietary supplement manufacturing firm's commitment to quality. The study emphasizes that compliance with 21 CFR 111 standards helps firms to maintain consistency and quality in dietary supplements manufactured in or exported to the US. This review also suggests that manufacturers must adhere to current Good Manufacturing Practices (cGMP) to ensure accurate ingredient identity, potency, purity and composition. Manufacturers are required to follow written procedures for various operations outlined in each subpart of 21 CFR Part 111. Compliance with these subparts ensures adherence to he regulatory requirements. Therefore, dietary

supplement manufacturers can demonstrate their commitment to quality by implementing a robust quality system in accordance with the provisions of 21 CFR Part 111.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CFR: Code of Federal Regulations; **cGMP:** Current Good Manufacturing Practices; **DSHEA:** Dietary Supplement Health and Education Act; **FDA:** Food and Drug Administration; **GMP:** Good Manufacturing Practices; **QMS:** Quality Mangagement Systems; **SOPs:** Standard Operating Procedures; **US:** United States.

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