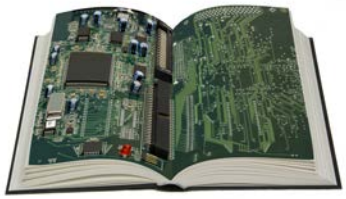
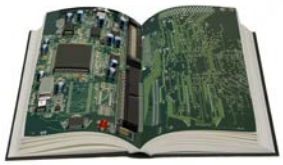


Part 211 Drug GMP e-Textbook

Table of Contents

(table of contents continued on following page)



Part 211 Drug GMP e-Textbook (Continued)

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Subpart B—Organization and Personnel

This article provides numerous considerations and examples for successfully complying with Part 211 Subpart B – Organization and Personnel. All requirements are reviewed for these regulations below, including:

- 211.22 – Responsibilities of Quality Control Unit
- 211.25 – Personnel Qualifications
- 211.28 – Personnel Responsibilities
- 211.34 – Consultants

Introduction

It can be said that people are the most important factor in Good Manufacturing Practice (GMP) compliance. They write the procedures, handle and test components, container closures, in-process materials, packaging materials, labeling and finished product. They also manufacture the product and complete the required documentation and records. The degree of accuracy to which these actions are accomplished is directly related to their knowledge, skill and training. Well-qualified and trained individuals make few mistakes, and assure a suitable level of compliance with GMP.

211.22—Responsibilities of Quality Control Unit

GMP regulation 211.22 spells out the requirement that a Quality Control Unit be established, and details the authority and responsibilities that are assigned to it. The purpose of the regulation is to assure that there is an independent group to evaluate materials, product and procedures without influence from groups involved in other aspects of product manufacturing. During inspections, Food and Drug Administration (FDA) investigators will want to see this independence demonstrated. The investigator will often ask for an organizational chart to verify that the Quality Unit does not report to the Manufacturing Department at any point in the organizational structure.

Quality Assurance or Control Responsibilities and Authority

This regulation states that the Quality Unit has both responsibility and authority. This is an important point to understand. The responsibility for review, testing or inspection is different than the authority to approve or reject materials or product.

For example, the Quality Unit has the responsibility to test drug products prior to release for distribution. It also has the authority to reject the drug product if it does not meet specifications.

Here are more examples of the Quality Unit's responsibilities and authority:

- Approve or reject components, container/closures, in-process materials, packaging materials, labeling and drug products
- Review batch production records to assure accuracy, and if any errors are detected, have the errors investigated
- Approve drug products manufactured or packaged by a contract company. These products are released under the Quality Unit's authority after testing and review of the contractor's finished product

Quality Unit's Facilities

Under normal circumstances, a drug manufacturing facility will have various areas set aside for use by the Quality Unit. These are in the form of offices, inspection stations and laboratories. GMP regulation 211.22 requires that such space be made available to the Quality Unit. The regulation also requires that these spaces be large enough, so that review, inspection and testing activities can be performed properly.

Other Quality Unit Responsibilities

The Quality Unit is also assigned to review and approve all procedures and specifications that have a direct impact on the drug product's identity, strength, purity and quality. This includes test methods, inspection procedures, manufacturing procedures, cleaning agents, etc. The list is all inclusive.

The final requirement for GMP compliance with this regulation is that all Quality Unit procedures and responsibilities be in writing. This eliminates any confusion.

211.25—Personnel Qualifications

Introduction

The importance of experience, knowledge and training of individuals involved in all aspects of drug manufacturing cannot be understated. Experienced, knowledgeable and well-trained personnel are the key factor to GMP compliance. They should perform their assigned tasks effectively, efficiently and with fewer errors than untrained personnel. This is why personnel qualifications is an area that FDA expects to be in full compliance.

Qualifications

This regulation requires that any person involved in the manufacture, processing, packaging, or handling of a drug product have the education, experience, or training, or a combination of these, to perform assigned functions. The ability to perform a task involves the interaction of education, experience and training. Simply stated, this means that an individual must know what to do and how to do it. This is the basis of qualification. Consider education as that which has prepared one to perform some future function. Training is that which prepares one to do a

specific function. Experience is having performed that or similar functions. Knowledge is the combination of all three.

For example, a facility microbiologist would have education in the biological sciences, training in environmental monitoring for the facility and experience working with microorganisms. This would be the knowledge base for this individual.

Training

A pharmaceutical manufacturer's training program must be in compliance with GMP regulation 211.25. The training of personnel must consist of training in the operations performed, in written procedures related to these functions, in GMP regulations Parts 210 and 211, in general, and those regulations in 210 and 211 specific to the functions performed.

Work-Specific Training

Work-specific training is training provided to enable an individual to properly perform the functions to which they are assigned. This type of training often involves having the individual observe the functions being performed, reading the written procedures related to the functions, assigning a trainer to explain the functions, how to do them, and observing and documenting the trainee's ability to accurately perform them. The trainer will often have a list of important steps in the assigned function that must be mastered. After all the steps are mastered, the training is complete, and the trainer then releases the individual to work under normal supervision. For example, if the function is batch record review, a trainer would be assigned and have the trainee observe a review being done. The trainee would be required to read all procedures applicable to batch record review, and then conduct a batch record review under the supervision of the trainer. When the trainer believes that the trainee is proficient in batch record review, the trainee is "released," and allowed to conduct batch record reviews under the same supervision as others doing such reviews.

GMP Training

GMP regulation 211.25 calls for employees to be trained in GMP regulations. This GMP training must be in GMP in general, as well as GMP regulations that specifically apply to the functions to which the individual is assigned.

General GMP Training

This type of GMP training is generally an overview that often includes a history of GMP, its purpose, importance of GMP in drug manufacturing, FDA's role in enforcing GMP regulations and importance of the individual in understanding and complying with these regulations. This type of GMP training is designed primarily for new employees who are not familiar with GMP. This type of training can be given to all employees periodically as a "refresher "course to keep all employees familiar with basic concepts of GMP regulations. GMP training must be conducted by qualified individuals.

GMP Specific Training

The other GMP training that is required is training an individual in GMP regulations directly applicable to the task performed. Written procedures required by GMP regulations in Parts 210 and 211 must also be included. Therefore, an individual working in the labeling department must be trained in GMP regulations contained in Subpart G—Packaging and Labeling, and in all of the written procedures required by this subpart specific to labeling and label control. It should be noted that this GMP training must also be done by qualified personnel on a frequent basis for employees to remain familiar with requirements in GMP regulations Parts 210 and 211.

Documentation For Training

A final point to consider is documentation of both work-related training and GMP training. GMP regulations require there be accurate records documenting the training of each individual for these types of training. In addition, the facility's training program must also be documented. This would be done by written procedures and policies describing how training is conducted and documented. As part of the training program, there needs to be a description of how the effectiveness of training is evaluated. Error rates, employee evaluations and trainee input and opinion are a few ways that effectiveness can be measured.

Supervisor Qualifications

GMP regulation 211.25 specifies that supervisory personnel must have the education, training, experience, or a combination of these, to perform assigned functions to assure the drug product has the safety, integrity, strength, quality and purity it claims to have. A supervisor in a drug manufacturing facility must be competent in several, usually related, manufacturing functions. This requires the qualifications of supervisory personnel to be more extensive than non-supervisory personnel, because of the larger variety of functions that are involved. A supervisor must have the knowledge to know if a function or task is performed improperly. A Packaging Department Manager must be knowledgeable in all packaging functions, whereas a filling machine operator is concerned with only the filling operation.

Number of Employees

The final requirement of the 211.25 regulation is related to the number of employees and supervisors assigned to manufacturing a drug product. Lack of a sufficient number of employees will result in more mistakes and mix-ups than that of a properly staffed facility.

211.28—Personnel Responsibilities

Introduction

Compliance with GMP regulation 211.28 involves individuals in various manufacturing areas practicing procedures and actions that are designed to minimize the potential of contamination to the product. These practices involve wearing protective clothing, sound sanitation and health

habits, entering limited access areas only if authorized, and reporting health conditions, such as open wound or lesions to their supervisor. By following such practices, the individual employee is in compliance with this GMP regulation.

Clothing

A specific requirement of GMP regulation 211.28 is for employees involved in the manufacturing process to wear appropriate and clean clothing. There should be written procedures that describe this clothing, frequency of changing or cleaning, and actions to be taken if clothing becomes soiled. Examples of appropriate clothing would include; lab coats, uniforms or coveralls. Frequency of changing could include daily, weekly, or some other specified time, need for a clothing change other than time would include; excessive accumulation of dust or dirt, oil or grease, leaving an aseptic processing area and entering a non-sterile area.

Protective Apparel

Protective apparel is worn in addition to clean clothing. It includes head coverings, face coverings, gloves and arm covers when long-sleeve clothing is not worn. Protective apparel provides protection for the following:

- The product from human contamination, such as the head and body hair
- The individual from direct contact with active ingredients and in-process materials that can be absorbed through the skin, eyes, mouth or nose
- Cleaning agents and solvents that may cause burns

Here is an example of the need for protective apparel. Hair is a common contaminant, but most hair is not lost from the head of an individual, but from the arms. This is the reason long sleeves or arm coverings are required, as well as head and face coverings.

Sanitation and Health Habits

Sound sanitation and health habits are common practices seen in food service, food processing, and of course, pharmaceutical manufacturing. They include washing hands after using washing and toilet facilities (restrooms), trimming and cleaning fingernails, flushing toilets after use and keeping the use of cosmetics to a minimum. Removing exposed jewelry is also a good practice. Following these practices will minimize contamination.

Limited Access Areas

Limited access areas are intended to limit contamination and the possibility of a labeling mix-up. Limited access areas would include; labeling storage and issuances, aseptic processing, and areas where powders tend to be generated, such as blending and milling. Another example would be areas where controlled substances are manufactured. Limited access results in only authorized personnel being present, so the number of individuals is restricted to those with specific reasons for being there. This reduces the possibility of cross-contamination with in-

process materials from different products, or a mix-up of labeling from different products. A label room is an example of a limited access area. Access is restricted to supervisors, labeling personnel and Quality. These individuals understand how to con-trol labeling to prevent mix-ups. A tablet machine operator would not. This is why label rooms are restricted access areas.

Health Conditions

The final requirement in GMP regulation 211.28 is concerning health conditions, such as unprotected wounds, abrasions, or flu of employees that can have a direct, adverse impact on components, container/closures, in-process materials or drug product. Any employee that has such a condition must be excluded from manufacturing operations in which the employee could have direct contact with any of the items mentioned. This regulation requires any health condition that could have an adverse impact be reported to the individual's supervisor. The supervisor must decide if the condition is a problem, and if so, assign that individual to reviewing records or other activity not involving the manufacture of the product.

To illustrate this point, an individual comes to work with symptoms of the flu (coughing, sneezing, watering eyes). The individual goes to the supervisor and reports not feeling well. The supervisor observes the symptoms and informs the individual to go home (take a sick day), and return when the flu is gone. The action of the individual and supervisor is compliant with this regulation. The individual reported his condition and the supervisor told the individual to go home.

211.34—Consultants

Introduction

This regulation is brief and concise regarding the requirements of qualifications for a consultant and what records need to be kept.

Qualifications

Qualification requirements for consultants are the same as those for the facility's employees. The consultant must have the education, training, experience, or a combination of them in the subject or area for which they are advising. If the subject or area involves the drug manufacturing process, then a knowledge of GMP regulations is also required.

Records

If a company has used a consultant, then a record of this consultant and services provided must be kept. The record must contain, at a minimum, the consultant's name, address, qualifications and type of service provided. Failure to maintain records of this nature is a violation of GMP regulations.

References

- 21 CFR Part 210 – Current Good Manufacturing Practice In Manufacturing, Processing, Packing, or Holding of Drugs: General
- 21 CFR Part 211 – Current Good Manufacturing Practice For Finished Pharmaceuticals
- FDA Guide to Inspections of Dosage Form Drug Manufacturer's—CGMPR's

Subpart B: Organization and Personnel
Auditing Checklist

211.22 – Responsibilities of Quality Control Unit

- ☐ Review Quality Unit procedures and verify reporting structures:
  - ☐ Evaluate this structure to determine the independence of the Quality Unit. A direct report to the manufacturing operation is questionable
- ☐ Review Quality Unit procedures in terms of authority and responsibilities:
  - ☐ Ask for samples of records that demonstrate this authority and responsibility, such as material and product testing, and batch record review
- ☐ Tour the facility and locate the Quality Unit's offices, labs, and inspection stations. The number and size should be adequate to perform assigned responsibilities
- ☐ Select samples of quality procedures and observe if they are being followed correctly

211.25 – Personnel Qualifications

- ☐ Ask to see written policies and procedures for training at the facility:
  - ☐ Evaluate them for adequacy in work-related tasks and GMP-related training
  - ☐ How is training effectiveness evaluated?
- ☐ Take a sampling of employee training files:
  - ☐ Review each file and verify that work-specific training matches:
    - ☐ Assigned function
    - ☐ GMP training
    - ☐ Frequency of training
- ☐ Select individual employees and interview each to evaluate:
  - ☐ Work-specific knowledge
  - ☐ Understanding of GMP regulations
  - ☐ Their assessment of the quality of the training they have received
- ☐ Ask for a list of the individuals who conduct GMP training:
  - ☐ Determine if they are qualified
- ☐ Review examples of training materials and their content:
  - ☐ Determine if materials are adequate for the intended content instruction
- ☐ Review qualifications of supervisors and department managers:
  - ☐ Their education, training and experience should be consistent with their responsibilities
- ☐ Tour the facility:
  - ☐ Evaluate if there is adequate personnel present to properly perform various manufacturing operations. You should not see individuals hurrying to complete their tasks