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Introduction to the FDA Current Good Manufacturing Practices (CGMPs) for Pharmaceuticals

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Introduction to the FDA Current Good Manufacturing Practices (CGMPs) for Pharmaceuticals

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1. Introduction

This course provides an introduction to the FDA Current Good Manufacturing Practices (CGMPs) for Pharmaceuticals. CGMPs are the foundation for producing drugs and medicines in a manner compliant with the FDA requirements. CGMPs, also called "Part 210 & 211", are the mandatory minimum requirements for manufacturing any product identified as a drug.

These CGMP requirements are intended for manufacturers to prove their drug products perform as intended and are safe for patients. The CGMPs are available to everyone and can be found at www.fda.gov. Despite the title, CGMPs reach far beyond the manufacturing or production floor. CGMPs contain requirements for buildings, facilities, equipment, packaging, labeling, warehousing, storage, raw materials, distribution, laboratory controls, and more. Documented evidence and detailed records are required as proof the drug products are being manufactured in compliance with CGMPs.

CGMPs are regulations and contain the MINIMUM requirements for drug facilities where theses activities occur: manufacturing, processing, packaging, or holding of a drug.

The learning objectives for this course are:

- Be aware of the FDA CGMPs for pharmaceuticals
- Understand the overall intent of the FDA CGMPs for pharmaceuticals
- Learn the definition of a drug
- Learn the contents of the general pharmaceutical CGMPs, 21 CFR Part 210

- Learn the 11 subparts of the pharmaceutical CGMPs, 21 CFR Part 211
- Be familiar with where to find the CGMPs at www.fda.gov
- Learn the CGMP requirements for Buildings & Facilities, Equipment, and Production
- Learn the CGMP requirements for Packaging, Label Control, Warehousing, and Distribution
- Understand the criticality of records and documentation

The information contained in this course is in no way intended to be recommendations or advice. It is important to seek professional consultation about a specific area, rather than use the general information provided in this course.

2. Intent of CGMPs

The overall intent of the CGMPs is patient and public safety, which is paramount to the FDA. For patient safety, CGMPs focus on the controls of facilities and practices involved with manufacturing, processing, packing, or holding of drugs. The controls in place must ensure identity, strength, quality, safety, and purity of the drug.

An overview of CGMPs can be found online at this link to fda.gov information:

Facts About FDA Current Good Manufacturing Practices (CGMP)
https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm

If the link above has changed or moved, search this term in a search engine: "FDA CGMP".

2.1. Taste of Raspberries, Taste of Death; The Sulfanilamide Disaster

The origins of the CGMPs come from tragedy and the FDA's dedication to patient safety is justified by history. The FDA began with the 1906 Pure Food and Drugs Act, while the name "FDA" was not assigned until 1930. The 1906 Act arose out of

public outcry following horrifying exposés on the meat packing industry.

Sources:
https://www.fda.gov/aboutFDA/WhatWeDo/History/
https://www.fda.gov/aboutfda/transparency/basics/ucm214403.htm

If the link above has changed or moved, search this term in a search engine: "Origins of FDA".

In 1937, more than 100 people in 15 states (many of them children) died from consuming a liquid medicine, which was clearly unsafe. The active ingredient, Sulfanilamide, had been dissolved in a sweet-tasting liquid, diethylene glycol (commonly known as antifreeze).

"The new formulation had not been tested for toxicity. At the time the food and drugs law did not require that safety studies be done on new drugs. Selling toxic drugs was, undoubtedly, bad for business and could damage a firm's reputation, but it was not illegal."

"The drug and the deaths led to the passage of the 1938 Food, Drug, and Cosmetic Act, which increased FDA's authority to regulate drugs."

Source:
https://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/

If the link above has changed or moved, search this term in a search engine: "taste of raspberries taste of death FDA".

2.2. Thalidomide Disaster – FDA SUCCESS

Thalidomide is a drug approved for use in western Europe in the early 1960s, which caused THOUSANDS of severe birth defects in babies, many with extremely deformed limbs. The drug was NOT approved in the US because a medical officer,

Dr. Frances Kelsey, discovered it hadn't yet been tested on pregnant animals – despite being widely used and sold in many countries. The FDA prevented a "public health tragedy of enormous proportions" in the United States. The US was protected by the FDA.

"Dr. Kelsey's reaction to thalidomide exemplifies the FDA's mission: **protecting and promoting the health of the American people, using science for regulatory decision-making.**"

The thalidomide tragedy led to public outcry for stronger regulations. These new regulations required manufacturers to prove their drugs were safe and effective; science became the basis for drug approvals. The science standards and expectations were raised. Companies were required to monitor the safety of their drugs AFTER being sold – by monitoring reports from those patients taking their medications. The manufacturers' responsibilities did not end once the product was sold.

"Companies had to monitor safety reports that emerged postmarket and adhere to **good manufacturing practices** that would lead to **consistently** safe products."

For the first time, companies started research and development functions for what we know now as clinical trials. This scientific rigor led to the most effective drugs being used most, rather than only those relying on extensive marketing. This is a huge benefit to both patients and the drug manufacturing industry.

When Thalidomide was denied approval in the US more than 50 years ago, the FDA proved to be leading the way in regulatory oversight of drugs. The world took notice then and the FDA remains a global leader in the regulatory arena.

Sources:
https://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm

https://blogs.fda.gov/fdavoice/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters/

If the links above has changed or moved, search this term in a search engine: "Thalidomide FDA history".

2.3. FDA's Science Based Decision-Making

Many of us do not remember a time when the FDA was not focused on science and data. We are all familiar with medications being in clinical trials. We have all seen the extensive labels with the long list of side effects. We are quite fortunate to have this information required before approval and readily available. There was a time, before the 1960's, when drug approvals did not require data or proof they were safe. The 1960's were not all that long ago, yet the FDA's science-based approval systems are now rigorous.

The length of time and the money spent prior to drug approval is a much-debated topic. The Internet contains numerous complaints of patients waiting for treatments and cures to be approved. Patients express frustration with promising medications going through years of clinical trials. Companies complain about the time and huge costs of getting medications approved. Incurring massive costs before anything is getting sold can seem unnecessary to some. However, the FDA's requirements for scientific proof of safety and effectiveness are for everyone's benefit.

"...in some circles regulation is viewed as a roadblock to innovation and economic growth. But in actuality, when done right, **regulation isn't a roadblock; it's the actual pathway to achieving real and lasting innovation**.

Smart, science-based regulation instills consumer confidence in products and treatments. It levels the playing field for businesses. It decreases the threat of litigation. It prevents recalls that threaten industry reputation and consumer trust, not to mention levying huge preventable costs on individual companies and entire industries. And it spurs industry to excellence."

Source:
https://blogs.fda.gov/fdavoice/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters/

If the links above has changed or moved, search this term in a search engine: "Thalidomide FDA history".

3. Definition of a "Drug"

CGMPs are regulatory requirements of all facilities involved with manufacturing, processing, packaging, or holding of a drug. "Drug" applies the to the traditional pharmaceutical products prescribed by a medical doctor. However, many treatments purchased at a drug store without a prescription (called Over the Counter Drugs) are "drug" products, as categorized by the FDA.

The FDA defines a "drug" as the following:

"Drug

A drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

Drug Product

The finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients."

Source:
https://www.fda.gov/drugs/informationondrugs/ucm079436.htm#D

If the link above has changed or moved, search this term in a search engine: "definition of drug FDA".

Anything used to diagnose, cure, mitigation, treat, or prevent a disease is a drug and must comply with CGMPs. Any substance (foods excluded) intended to affect the structure or any function of the human body is a drug and must comply with CGMPs.

Many everyday products are categorized as "drugs" and must comply with CGMPs. Often the general public, and even users/consumers/ patients, are not aware they are using drug products, especially when the products are purchased without a prescription. Drugs purchased without a prescription are called Over-the-Counter-Drugs (OTCs). Many OTC products are used in a typical household without the understanding they are actually drugs. Most people recognize pills, tablets, and capsules for pain relief (like ibuprophen and aspirin) are drugs. However, most families don't know sunscreen is a drug.

Below are some products many people don't realize are categorized as drugs:

- Sunscreens, including some cosmetics
- Acne creams, including anything purchased at the drug store with a claim to treat or mitigate acne
- Topical medicated creams
- Numbing sprays, like Chloraseptic
- Throat lozenges with claims to treat or soothe soreness
- Medicated shampoos to treat dandruff
- Decongestants
- Antihistamines
- Allergy medication
- Anti-diarrhea medication, like Pepto-Bismol. Fun fact: Pepto-Bismol contains bismuth, which is why the "Bismol" name was chosen
- Fluoride toothpaste
- Antiperspirants

There are products sold and marketed without even the company recognizing they are drugs. In these instances, the FDA notifies the companies through official channels, often with severe outcomes. One of the enforcement actions available to the FDA is called a "warning letter". Non-confidential information about warning letters and other enforcement actions is available at fda.gov. Below is an excerpt from an

actual warning letter issued to a company for selling a drug product not identified as a drug.

"This is to advise you that the Food and Drug Administration (FDA) reviewed your website at the Internet address http://healthyhabits.com/ in October 2016 and has determined that you take orders there for the products Dermatox Ointment 1.7 oz and DermaTox® - 4 oz. The claims on your website establish that the products are drugs under sections 201(g)(1)(B) and/or 201(g)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(B) and/or 21 U.S.C. § 321(g)(1)(C)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or articles intended to affect the structure or any function of the human body. As explained further below, introducing or delivering these products for introduction into interstate commerce for such uses violates the Act."

The full warning letter can be found at the following link: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm544064.htm

If the link above has changed or moved, search this term in a search engine: "FDA warning letter 2016".

4. Contents of General CGMPs, Part 210

Part 210 contains the general information about CGMPs. Part 210 serves as an introduction to the details contained in Part 211. Part 210 contains three sections; Sections 210.1, 210.2, 210.3, titled at the FDA website as:

"Sec. 210.1 Status of current good manufacturing practice regulations."

"Sec. 210.2 Applicability of current good manufacturing practice regulations."

"Sec. 210.3 Definitions."

In addition to general requirements, Part 210 Section 1 states failure to comply with CGMPs can result in regulatory action, **including actions against the person who is responsible**.

Source: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210&showFR=1

If the link above has changed or moved, search this term in a search engine: "FDA Part 210 section 1".

It can be tempted to skip over Section 210 because it contains general information, not specifics of the requirements. However, Section 210 contains essential information needed to understand the CGMPs. Some important items to note from Section 210:

- Part 211 applies to drugs. (See Section 3 of this course for the definition of a drug.)
- Biological products for human use are covered in Parts 600 to 680. (There is a distinction between drugs and biological products.)
- Only applicable parts must be followed. For example, if a company only performs warehousing, only the sections pertaining to warehousing are required.

The definitions section is a valuable resource for interpreting and implementing CGMPs. Many terms can be used in slightly different ways across industries and companies. What looks like a general term can mean something quite specific to the FDA. Some definitions to note are below:

- *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.
- *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

- *Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products.
- *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
- *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).
- Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

4.1. Biological Products

Most of the public is quite familiar with a few types of biological products, vaccines and allergy shots, but think of them as drugs; not recognizing them as biological products.

The FDA defines a biological product as:

"Biological products, or biologics, are medical products. Many biologics are made from a variety of natural sources (human, animal or microorganism). Like drugs, some biologics are intended to treat diseases and medical conditions. Other biologics are used to prevent or diagnose diseases."

Biological products are often incorrectly thought to be drugs, but the FDA classifies them differently. Vaccines, especially, are considered drugs by the general public, but they are actually biological products. Biological products include:

- "vaccines
- blood and blood products for transfusion and/or manufacturing into other products

- allergenic extracts, which are used for both diagnosis and treatment (for example, allergy shots)
- human cells and tissues used for transplantation (for example, tendons, ligaments and bone)
- gene therapies
- cellular therapies
- tests to screen potential blood donors for infectious agents such as HIV"

Source:
https://www.fda.gov/aboutfda/transparency/basics/ucm194516.htm

If the link above has changed or moved, search this term in a search engine: "definition of biological product FDA".

Biological products are excluded from the drug CGMPs in Parts 210 and 211. Biological products are covered in Parts 600 through 680. The FDA distinguishes biological products from drugs and pharmaceuticals. Per the FDA, biological products differ from conventional drugs:

How do biologics differ from conventional drugs?

"Most drugs consist of pure chemical substances and their structures are known. Most biologics, however, are complex mixtures that are not easily identified or characterized. Biological products differ from conventional drugs in that they tend to be heat-sensitive and susceptible to microbial contamination. This requires sterile processes to be applied from initial manufacturing steps."

Source:
https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048341.htm#Howdobiologicsdifferfromconventionaldrugs

If the link above has changed or moved, search this term in a search engine: "difference between biologics and conventional drugs FDA".

Biologics companies are required to follow a set of rules (in Parts 600 to 680) to ensure safety and satisfy consistent criteria, but not the exact CGMPs in Parts 210 & 211.

For more information about biological products:
https://www.fda.gov/AboutFDA/Transparency/Basics/ucm193816.htm

If the link above has changed or moved, search this term in a search engine: "FDA basics on vaccines blood and biologics".

5. Contents of CGMPs, Part 211

Part 211 contains eleven Subparts, A through K, with the requirements for CGMPs for pharmaceuticals. The CGMPs contain legal requirements, not specification or details of how to comply. The Subparts of Part 211 contain the requirements for the minimum controls, not the details of parameters to monitor; how to implement or maintain the controls is also not included. Compliance with CGMPs can be accomplished in many different ways. This can be frustrating to some because direct mandates with specifications are clearer in some instances; however, the CGMPs apply to millions of operations, thus cannot dictate exact dimensions/specifications/measurements because of the necessary differences in industry.

The Subparts of Part 211 as listed by the FDA are:

Subpart A--General Provisions
- § 211.1 - Scope.
- § 211.3 - Definitions.

Subpart B--Organization and Personnel
- § 211.22 - Responsibilities of quality control unit.
- § 211.25 - Personnel qualifications.
- § 211.28 - Personnel responsibilities.
- § 211.34 - Consultants.

Subpart C--Buildings and Facilities
- § 211.42 - Design and construction features.
- § 211.44 - Lighting.
- § 211.46 - Ventilation, air filtration, air heating and cooling.
- § 211.48 - Plumbing.
- § 211.50 - Sewage and refuse.
- § 211.52 - Washing and toilet facilities.
- § 211.56 - Sanitation.
- § 211.58 - Maintenance.

Subpart D--Equipment
- § 211.63 - Equipment design, size, and location.
- § 211.65 - Equipment construction.
- § 211.67 - Equipment cleaning and maintenance.
- § 211.68 - Automatic, mechanical, and electronic equipment.

§ 211.192 - Production record review.
§ 211.194 - Laboratory records.
§ 211.196 - Distribution records.
§ 211.198 - Complaint files.

Subpart K--Returned and Salvaged Drug Products

§ 211.204 - Returned drug products.
§ 211.208 - Drug product salvaging.

Source:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

If the link above has changed or moved, search this term in a search engine: "Part 211 FDA".

It should be noted any skipped numbers are intentional. For example, there is no Section 211.2. While Sections 211.1 and 211.3 exist, there is no Section 211.2.

5.1. Importance of Quality Assurance

Subpart B, Organization and Personnel, is a principal portion impacting every over part of the CGMPs. Subpart B requires a quality control unit be established. This quality control unit, often called the Quality Assurance Department (QA), is required to have the responsibility and authority to approve or reject all components (such as raw materials), drug product containers, packaging material, and drug product. Quality Assurance must have the authority to review production records for errors and verify any errors are fully investigated. Subpart B also states the responsibilities and procedures applicable to quality are required to be in writing.

"Sec. 211.22 Responsibilities of quality control unit…

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed."

Source:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.11.2

If the links above has changed or moved, search this term in a search engine: "Part 211 FDA".

The role of Quality Assurance (QA) is one of the most crucial portions of the CGMPs and all FDA's governance. The QA responsibilities are also one of the most misunderstood components of CGMPs. The role of a quality unit in an FDA-regulated industry differs drastically from the non-regulated environments. In an FDA-regulated facility, QA is responsible for much more than a Quality department in an unregulated industry. The FDA expects QA to oversee all CGMP activities at some level. While the general term "quality control unit" is used in the CGMPs, there is a difference between Quality Control (a laboratory and associated testing) and Quality Assurance (responsibly for the quality systems and all CGMP elements).

The FDA defines this difference:

"QC usually involves (1) assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products; (2) evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits; and (3) determining the acceptability of each batch for release.

"QA primarily involves (1) review and approval of all procedures related to production and maintenance, (2) review of associated records, and (3) auditing and performing/evaluating trend analyses."

The concept of independence is vital in an FDA-regulated facility. Independence is often interpreted to mean the QA department does not report directly to or through the manufacturing department/unit.

"Under a quality system, it is normally expected that the product and process development units, the manufacturing units, and the QU will remain independent. "

Source:
https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf

If the links above has changed or moved, search this term in a search engine: "role of QA in CGMPs FDA".

6. Where to Find CGMPs

CGMPs are available to EVERYONE with an Internet connection. Memorization is not expected and those in the drug industry reference them often at the following links.

21 CFR Part 210
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.1

21 CFR Part 211
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

If the links above has changed or moved, search this term in a search engine: "Part 210 and 211 FDA".

The FDA's website, www.fda.gov, is a wealth of information for numerous topics. Try the search function for anything related to foods, drugs, medical devices, and more. This course contains many links to fda.gov pages to get you started.

7. CGMPs for Buildings & Facilities, Equipment, and Production

The CGMPs for Buildings & Facilities, Equipment, and Production are contained in Part 211, Subparts C, D, and F. These Subparts are extremely relevant to the work many engineers perform.

7.1. Subpart C; Buildings & Facilities

The focus of Subpart C is the design, upkeep, and maintenance of the structures involved with the manufacturing, processing, packaging, and warehousing of drug products. The core of Subpart C is requiring the buildings have adequate space, temp/humidity controls, lighting, sewage drains, cleaning, clean toilets for employees, water for employee to use for personal cleanliness, and repairs.

There are eight Sections in Subpart C:

Subpart C--Buildings and Facilities
§ 211.42 - Design and construction features.
§ 211.44 - Lighting.
§ 211.46 - Ventilation, air filtration, air heating and cooling.
§ 211.48 - Plumbing.
§ 211.50 - Sewage and refuse.
§ 211.52 - Washing and toilet facilities.
§ 211.56 - Sanitation.
§ 211.58 - Maintenance.

It may surprise some people to find the FDA has regulations on sewage, trash, and toilets. However, it can directly impact the safety of a medicated cream if the sewers back-up into the manufacturing area. Patient and public safety is impacted if throat lozenges are handled by employees who don't have access to hand-washing facilities.

While much of the wording in Part 211 is vague and left to interpretation, like the words "adequate" and "timely", some Subparts contain detailed requirements. Subpart C includes details such as:

- Operations, including manufacturing and packaging, of penicillin must be performed in separate facilities from other drug products. (211.42)
- Sewage drains are required to have an "air break or other mechanical device to prevent back-siphonage". (211.48)
- Potable water must the standards in 40 CFR Part 141.
- Hot and cold water must be provided to employee washing facilities. (211.52)

- Soap or detergents must be provided to employee washing facilities. (211.52)
- There must be written procedures for the use of rodenticides, insecticides, and cleaning agents. (211.56)

In addition to Subpart C, the FDA issued guidance for documenting production and manufacturing. In the "Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations", FDA states:

"Under a quality system, the technical experts (e.g., engineers, development scientists), who have an understanding of pharmaceutical science, risk factors, and manufacturing processes related to the product, are responsible for defining specific facility and equipment requirements.

Under the CGMP regulations, the quality unit (QU) has the responsibility of reviewing and approving all initial design criteria and procedures pertaining to facilities and equipment and any subsequent changes (§ 211.22(c))."

Source:
https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf

If the link above has changed or moved, search this term in a search engine: "FDA CGMP Guidance 2006".

7.2. Subpart D; Equipment

The focus of Subpart D is the adequacy of the equipment for the intended use, including design, cleaning, and maintenance. The core of Subpart D is the equipment should be adequate to manufacture the products in regards to size, material, cleanliness, "cleanability", sanitization, and preventive and corrective maintenance.

There are five Sections in Subpart D:

Subpart D--Equipment
§ 211.63 - Equipment design, size, and location.
§ 211.65 - Equipment construction.
§ 211.67 - Equipment cleaning and maintenance.
§ 211.68 - Automatic, mechanical, and electronic equipment.
§ 211.72 - Filters.

As with Subpart C, Subpart D contains some highly specific requirements, such as:

- A backup file of data entered into a computer system must be kept. Hard copies or alternative systems, such as duplicates, tapes, or microfilm, are required to assure the backup data are exact, complete, and secure from alteration, inadvertent erasures, or loss.
- An additional nonfiber-releasing filter with a maximum pore size rating of 0.2 micro (0.45 micron if the manufacturing conditions dictate) is required if a fiber-releasing filter is required. (211.72)

Subpart D contains a section on electronic equipment, 211.68, including equipment with a "computer". This section is not intended to be the sole laws or guidance on computer systems. Extensive considerations must be given when controlling a computerized system in a regulated environment. See section #9 of this course for information on electronic records and electronic signatures.

In addition to Subpart D, the FDA issued guidance for documenting production and manufacturing. In the "Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations", FDA states:

"Under the CGMP regulations, equipment must be qualified, calibrated, cleaned, and maintained to prevent contamination and mix-ups (§§ 211.63, 211.67, 211.68). *Note that the* ***CGMP regulations require a higher standard for calibration and maintenance than most non- pharmaceutical quality system models***. The CGMP regulations place as much emphasis on process equipment as on testing equipment (§§ 211.160, 211.63, 211.67, and 211.68) while most quality systems focus only on testing equipment."

Source:
https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf

If the link above has changed or moved, search this term in a search engine: "FDA CGMP Guidance 2006".

7.3. Subpart F; Production & Process Controls

The focus of Subpart F is the documentation and management of the manufacturing steps. The core of Subpart F is the requirement to have written procedures in place for controlling, documenting, and providing proof the manufacturing steps were followed; and investigations (aka deviations) when the steps are not followed as stated in the procedures.

There are eight Sections in Subpart F:

Subpart F--Production and Process Controls

§ 211.100 - Written procedures; deviations.
§ 211.101 - Charge-in of components.
§ 211.103 - Calculation of yield.
§ 211.105 - Equipment identification.
§ 211.110 - Sampling and testing of in-process materials and drug products.
§ 211.111 - Time limitations on production.
§ 211.113 - Control of microbiological contamination.
§ 211.115 - Reprocessing.

The formality of procedures and deviation investigations can be surprising to those who are new to an FDA-regulated facility. However, the requirements in Subpart F are expected to be formal, documented in detail, highly controlled, require formal approvals/ signatures, and provide rationale and justification for the decisions and changes made. The investigations are expected to have product impact assessments, review of any previous similar incidents, and put in place measures to prevent re-occurrence.

The word "deviation" is used as a general term in Subpart F; however, "deviation" is the exact word used in many facilities for when procedures are not followed. A deviation accompanies an investigation, including justification for any decisions made and corrective or preventive actions taken. Other terms are used in place of deviation, like discrepancy, variance, non-conforming event, and problem record, to name just a few. Regardless of the name, an accompanying investigation is required.

One of the vital parts of Subpart F is the requirement for highly detailed recording on the production processes. In many cases, this document is a procedure/form called a "batch record". All the items in sections 211.101, 103, 105, 110 111, 113, and 115 are required to be recorded in a batch record type document. This document can be paper, electronic, or a combination of both. Per 211.100, the quality control unit must approve the procedures containing the items required in Subpart F. More information on records can be found in Subpart J.

In addition to Subpart F, the FDA issued guidance for documenting production and manufacturing. In the "Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations", FDA states:

"In a modern quality systems manufacturing environment, the significant characteristics of the product being manufactured should be defined from design to delivery, and control should be exercised over all changes. In addition, quality and manufacturing processes and procedures — and changes to them — must be defined, approved, and controlled (§ 211.100). It is important to establish responsibility for designing or changing products. Documenting processes, associated controls, and changes to these processes will help ensure that sources of variability are identified.

Documentation includes:

- Resources and facilities used
- Procedures to carry out the process
- Identification of the process owner who will maintain and update the process as needed
- Identification and control of important variables
- Quality control measures, necessary data collection, monitoring, and appropriate controls for the product and process
- Any validation activities, including operating ranges and acceptance criteria
- Effects on related process, functions, or personnel"

Source:
https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf

If the link above has changed or moved, search this term in a search engine: "FDA CGMP Guidance 2006".

8. CGMPs for Packaging, Label Control, Warehousing, and Distribution

Many people are unaware CGMPs extend to packaging, label control, and warehousing/holding because often the focus of CGMPs is manufacturing. From a patient safety perspective, packaging, labeling, and warehousing are just as important as raw materials and manufacturing. Patients rely on accurate labels to know the identity of the drug and determine dosage. If the label contains the wrong drug name or dosage, patient safety could be seriously impacted, even resulting in death.

Warehousing directly impacts the efficacy of drug because incorrect storage conditions can cause drugs to be ineffective much earlier than the expiration date on the label. If a patient takes ineffective antibiotics, the impact could be huge. Expiration dates are determined for specific storage conditions, which are included on the labeling. If a pallet of antibiotics is stored at high temperatures in the months prior to shipping, the effectiveness might be compromised.

8.1. Subpart G; Packaging & Labeling Control

The focus of Subpart G is the requirements to follow written procedures for controls of labeling and packaging materials. The core of Subpart G is the labels/placards/packaging must be controlled at every step from arriving onsite through being affixed to a product or being destroyed. Expiration dating is also required.

There are six Sections in Subpart G:

Subpart G--Packaging and Labeling Control
§ 211.122 - Materials examination and usage criteria.
§ 211.125 - Labeling issuance.
§ 211.130 - Packaging and labeling operations.
§ 211.132 - Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
§ 211.134 - Drug product inspection.
§ 211.137 - Expiration dating.

Labeling is often overlooked as part of CGMPs because there can be a tendency to be solely focused on the manufacturing process; yet labeling can be one of the more complex and critical operations. Mislabeled drug products are cited by the FDA when discovered. The FDA issued a warning letter, a serious enforcement action, for a mislabeled (misbranded) product, with excerpts shown below.

"Consequently, the labeling of your AnodyneRx product fails to bear adequate directions for its intended use, causing it to be misbranded under section 502(f)(1) of the FD&C Act."

Source:
https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm511703.htm

If the link above has changed or moved, search this term in a search engine: "FDA warning letter 2016 labeling".

In addition to Subpart F, the FDA issued guidance for documenting packaging and labeling. In the "Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations", the FDA states:

"Packaging and labeling controls, **critical stages in the pharmaceutical manufacturing process**, are not specifically addressed in quality systems models. However, the Agency recommends that manufacturers always refer to the packaging and labeling control regulations at § 211 Subpart G. In addition — and this ***is*** consistent with modern quality systems — FDA recommends that, as part of the design process, before commercial production, the controls for all processes within the packaging and labeling system be planned and documented in written procedures. The procedures should outline quality control activities and the responsible positions. Specifications and controls for the packaging and labeling materials should also be determined before commercial production. Distinct labels with discriminating features for different products, such as a product marketed with different strengths, should be included to prevent mislabeling and resulting recalls."

Source:
https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf

If the link above has changed or moved, search this term in a search engine: "FDA CGMP Guidance 2006".

8.2. Subpart H; Holding & Distribution

The focus of Subpart H is the storage, quarantine/segregation, and distribution of drug products. The core of Subpart H is ensuring drugs are stored under appropriate conditions (temp, humidity, light, etc.), segregated to clearly identify what is acceptable to release, first-in-first-out warehousing, and detailed records of distribution in the event of a recall.

There are two Sections in Subpart H:

Subpart H--Holding and Distribution
§ 211.142 - Warehousing procedures.
§ 211.150 - Distribution procedures.

While short, Subpart H contains some powerful requirements like the requirement to distribute oldest products first and practices around quarantine. Quarantine is a term for keeping products and materials not yet ready for distribution separated from those items ready for release to patients, drug stores, or pharmacies. Quarantine is critical

to prevent the unintentional release of a drug product before the release criteria have been satisfied.

Subpart H also requires detailed distribution records to facilitate quick and efficient recalls. Recalls may be needed for multiple reasons and accurate records can be the difference between life and death.

9. Criticality of Records and Documentation

Part 211 Subpart J contains the requirements for "Records and Reports" at a high level. However, records and documentation are at the heart of every part of CGMPs. Records and documentation are the way to PROVE compliance with CGMPs. Compliance must be proven and documented; nothing is implied or inferred. It is often said in FDA-regulated industries, "If it isn't documented, it didn't happen." This is a light-hearted saying to demonstrate the importance of recording actions and events. If the event isn't documented, how can it be proven the event occurred? Patient safety must be proven, not assumed.

Subpart J Records and Reports contains the following:

Subpart J--Records and Reports

§ 211.180 - General requirements.
§ 211.182 - Equipment cleaning and use log.
§ 211.184 - Component, drug product container, closure, and labeling records.
§ 211.186 - Master production and control records.
§ 211.188 - Batch production and control records.
§ 211.192 - Production record review.
§ 211.194 - Laboratory records.
§ 211.196 - Distribution records.
§ 211.198 - Complaint files.

The importance of records and documentation cannot be over-emphasized. All the sections of Parts 211 involve documentation at some level. Documentation, procedures, recording of events, formal approvals, documenting rationale for investigations, and justifications for changes are woven throughout the CGMPs.

9.1. Electronic Records

The terms "documentation" and "signatures" are not limited to paper documents or ink/handwritten signatures. Compliance with CGMPs is required for electronic documents and paper documents. Electronic signatures are expected to be as binding as ink/handwritten signatures.

Most documents are in electronic format now, with more and more paper documents being eliminated every year. Many signatures are electronic and are governed by what has become known as "Part 11". Part 11 is the FDA law governing electronic signatures. There has been controversy regarding how the FDA initially attempted to govern and provide guidance for electronic documents. Much can be found on the Internet with a search of "FDA Part 11 Controversy".

The FDA's guidance for industry regarding electronic records and electronic signatures alludes to the "controversy" in the "Background section. In the Background section of FDA's Part 11 guidance, the following is stated:

> "In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.
>
> After part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. FDA has (1) spoken about part 11 at many conferences and met numerous times with an industry coalition and other interested parties in an effort to hear more about potential part 11 issues; (2) published a compliance policy guide, CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures; and (3) published numerous draft guidance documents including the following:
>
> - 21 CFR Part 11; Electronic Records; Electronic Signatures, Validation
> - 21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms

- 21 CFR Part 11; Electronic Records; Electronic Signatures, Time Stamps
- 21 CFR Part 11; Electronic Records; Electronic Signatures, Maintenance of Electronic Records
- 21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records

Throughout all of these communications, concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these concerns, we decided to review the part 11 documents and related issues, particularly in light of the Agency's CGMP initiative. In the Federal Register of February 4, 2003 (68 FR 5645), we announced the withdrawal of the draft guidance for industry, 21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records.
...

We are now re-examining part 11, and we anticipate initiating rulemaking to revise provisions of that regulation. To avoid unnecessary resource expenditures to comply with part 11 requirements, we are issuing this guidance to describe how we intend to exercise enforcement discretion with regard to certain part 11 requirements during the re-examination of part 11. As mentioned previously, part 11 remains in effect during this re-examination period."

FDA's Part 11 guidance and can be located at:

https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125125.pdf

If the link above has changed or moved, search this term in a search engine: "FDA Part 11 Guidance".

Regardless of any differing interpretations, electronic records are governed by the FDA in addition to paper records.

The laws for electronic records and signatures are contained in 21 CFR Part 11 (hence why it is called Part 11). The actual legal requirements for electronic records and electronic signatures include the following and can be viewed online at the FDA links below.

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A--General Provisions
§ 11.1 - Scope.
§ 11.2 - Implementation.
§ 11.3 - Definitions.

Subpart B--Electronic Records
§ 11.10 - Controls for closed systems.
§ 11.30 - Controls for open systems.
§ 11.50 - Signature manifestations.
§ 11.70 - Signature/record linking.

Subpart C--Electronic Signatures
§ 11.100 - General requirements.
§ 11.200 - Electronic signature components and controls.
§ 11.300 - Controls for identification codes/passwords.

Source:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11

If the link above has changed or moved, search this term in a search engine: “FDA Part 11”.

10.Remaining Subparts

Subparts A, B, E, I, K are not detailed in this course but may be relevant to some engineers working in industries regulated by Parts 210 & 211. These Subparts, and all Subparts, can be reviewed at fda.gov and at the online locations provided below and throughout this course.

- Subpart A; General Provisions
- Subpart B; Organization and Personnel

- Subpart E; Control of Components and Drug Product Containers and Closures
- Subpart I; Laboratory Controls
- Subpart K; Returned and Salvaged Drug Products

Source:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1

If the link above has changed or moved, search this term in a search engine: "21 CFR Part 211".

11. Summary

CGMPs are mandatory for drug manufacturers and include the minimum requirements for many areas outside the production floor, such as labels, employee toilets, and warehousing. All facilities involved with the manufacturing, processing, packaging, and warehousing of drug products must comply with CGMPs. Many products not generally recognized as drugs are categorized as drugs by the FDA, such as sunscreens and antiperspirants; therefore, these over-the-counter products must comply with CGMPs. The CGMPs are readily available and can be accessed by anyone at www.fda.gov. Records and documentation are the way to PROVE compliance with CGMPs, including electronic records. Compliance must be proven and documented; nothing is implied or inferred.

Engineers and the FDA share a common goal – public safety.