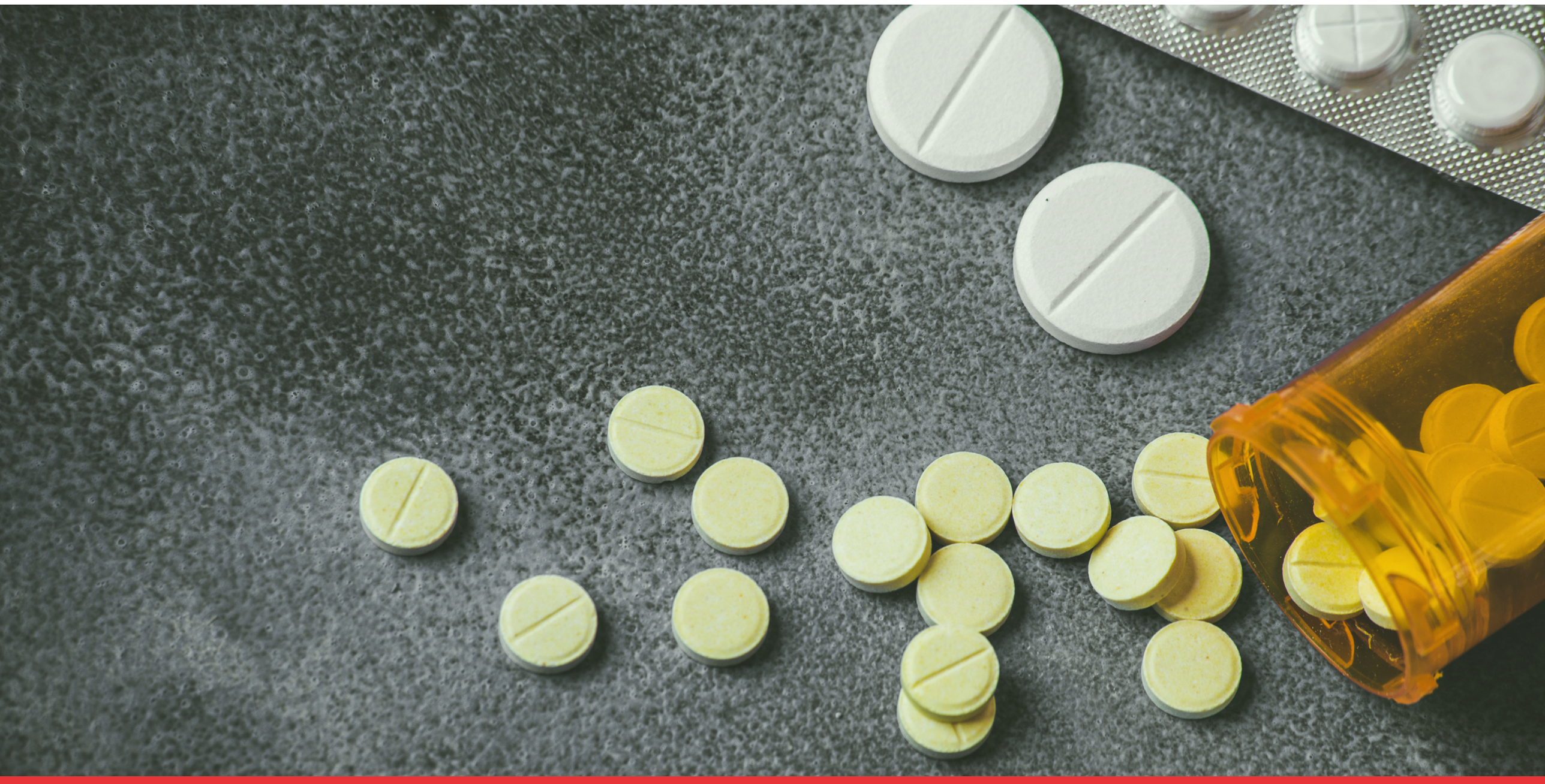
Cannabis & Hemp Safety Certification Requirements

Drug Add-On Module for
PJRFSI Hemp & Cannabis GMP Standard Version 2.0



Drug Add-On Module. Issued 1/25/2022. Revised n/a. Rev 1.0

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Introduction

Perry Johnson Registrars Food Safety, Inc. (PJRFSI) is committed to providing value-added food safety certification to clients. Our entire team believes that rigor and consistency during audit activities leads to higher levels of customer and end-user satisfaction. PJRFSI is dedicated to uphold the highest standards of professionalism, technical competence and integrity throughout the life cycle of the audit process. We apply the principles of quality management, collaboration and organizational excellence in all of our office and field activities and comply with the requirements set forth by the international standards organizations, accreditation bodies and other affected parties. Through this dedication, we have created and maintain a work environment which provides opportunities and a culture of continual improvement, learning and development for clients, auditors, staff and stakeholders within the food chain.

PJRFSI Dietary Supplement Add-On Module is based on FDA CFR 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements. This add-on module covers the manufacture of cannabis products that conform to the dietary supplement requirements. It is an add on module only and must be audited in accordance with Cannabis/Hemp Safety Standard for Manufacturing which includes the requirements set forth in the Management System and GMP Requirements & Other Pre-Requisite Program sections.

Drug Add-On Module Requirements

CFR 21 Sec 210.1 - Management Responsibilities to Meet Requirements

During the manufacture, processing, packing, or holding of a drug, a quality management system has been established to meet CFR 21 Parts 211 through 226 to assure that any such drug:

- meets the requirements of the act as to safety
- meets the requirements of the act identity and strength
- meets quality and purity characteristics it purports or is represented to possess

It should be understood by management at the organization that failure to comply with the requirements as set forth may be subject to regulatory action.

CFR 21 Sec 210.2

The applicability of the cGMP requirements should be determined in the quality management system including:

- regulations specifically applicable to the drug
- general requirements that must be met
- scope of compliance applicable to the drug

CFR 21 Sec 210.3

The quality management system must address the definitions defined in CFR 21 Section 210.3 either by reference or other means for items such as Batch, Lot Number, Active Ingredient, Inactive Ingredient, In-Process Material, Fiber, Percent Theoretical Yield, Quality Control Unit, etc.

CFR 21 Sec 211.1

The scope of the quality management system must identify the statutory and regulatory items including those that may be applicable in the cGMP to include:

- each applicable section requirement
- any exceptions described with reasons they may not be applicable to the drug
- in the event of any conflicting regulation, the regulation that most closely applies to the drug should be followed

CFR 21 Sec 211.3

The definitions from 210.3 of the regulation must be applied, with verification of such application.

CFR 21 Sec 211.22 - Responsibilities Quality Control Unit

A quality control unit must be available with the responsibility and authority to:
- approve or reject all materials and products
- review all production records for errors
- approve or reject all materials provided or held by contract by another organization

Adequate quality control unit laboratory facilities must be available for testing and approval or rejection of:
- components
- drug product containers
- closures
- packaging materials
- in-process materials
- drug products

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

The responsibilities and procedures related to the quality control unit should be in writing and adherence to them should be verified.

CFR 21 Sec 211.25 - Personnel Qualifications

Each person involved in the manufacture, processing, packing, or holding of a drug product should have education, training, and experience (or a combination of these) to enable said person to perform their assigned functions.

Training should occur for each person as follows:
- in particular operations the person performs
- in current good manufacturing practice (cGMP) requirements as related to their job functions
- in documented procedures related to the job functions

The training for cGMP should be conducted by qualified individuals on a continuing basis with sufficient frequency to ensure employees remain familiar with cGMP requirements relevant to them. This should be verified.

Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product should have the education, training, and experience (or a combination thereof) to perform assigned functions in such a manner to assure that the drug product has the safety, identity, strength, quality, and purity it purports or is represented to possess. This should be verified.

There should be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product. This should be verified.

CFR 21 Sec 211.28 - Personnel Responsibilities (Security)

Only personnel authorized by supervisory personnel should be permitted to enter those areas of the building and facilities designated as limited-access areas.

CFR 21 Sec 211.34 - Consultants

Consultants advising on the manufacture, processing, packing, or holding of drug products should have sufficient education, training, and experience (or a combination thereof) to advise on the subject for which they have been retained. Records of such consultants should be maintained, containing the name, address, and qualifications of said persons and the type of service(s) they have provided.

CFR 21 Sec 211.42

Buildings and facilities should include design and construction features to allow adequate space and separation for maintenance work to occur.

Adequately-sized, separated, or defined areas or such other control systems should be available as necessary to prevent contamination or mix-ups during the course of the following procedures:

- receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging
- storage of released components, drug product containers, closures, and labeling
- storage of in-process materials
- manufacturing and processing operations
- packaging and labeling operations
- quarantine storage before release of drug products
- storage of drug products after release
- control and laboratory operations

Aseptic processing should be completed and includes as appropriate:

- air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar
- a system for cleaning and disinfecting the room and equipment to produce aseptic conditions

CFR 21 Sec 211.46

If operations relating to the manufacture, processing, or packaging of penicillin are performed at the facility, these should be kept separate from other drug products for human use. This should include separate air systems.

Adequate ventilation, air filtration, air heating and cooling should be provided, including:

- equipment for adequate control over air pressure, micro-organisims, dust, humidity, and temperature provided as appropriate for manufacture, processing, packing, and holding of a drug product
- when air is re-circulated to production areas, measures should be taken to control recirculation of dust from production
- in areas where air contamination occurs during production, there should be adequate exhaust systems or other systems to control contaminants

CFR 21 211.48 - Plumbing

Potable water should meet the standards described in the Environmental Protection Agency's Drinking Water Regulations set forth in 40CFR part 141. Water not meeting the EPA Drinking Water Regulations should not be permitted in the potable water system.

CFR 21 211.52

Washing and toilet facilities should be adequate and provided with:

- hot and cold water
- air dryers or single-use towels

CFR 21 Sec 211.56 - Sanitation Including Pest Control

The building should remain free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities should be kept. Verification of these procedures being followed is required.

CFR 21 Sec 211.65

Any substances required for operation of equipment such as lubricants or coolant should be controlled adequately so as to not come into contact with components, drug product containers, closures, in-process materials, or drug products.

CFR 21 Sec 211.67

Written procedures should be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. At a minimum, these procedures should include:

- assignment of responsibility for cleaning and maintaining equipment
- a description in sufficient detail for the methods, equipment, and materials used in cleaning and maintenance operations, and the method of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance
- removal or obliteration of previous batch identification
- protection of clean equipment from contamination prior to use

Records should be retained of maintenance, cleaning, sanitizing, and inspection in accordance with subpart J sec 211.180 and 211.182.

CFR 21 Sec 211.68

Appropriate controls should be exercised over computer or related systems to ensure that changes in master production and control records (or other records) are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records and data should be checked for accuracy. The degree and frequency of checks should be appropriate to the complexity and reliability of the computer or related system. A backup file of data entered into the computer should be kept.

If any exceptions are made to the backup requirement as a result of where certain data, such as calculations performed in connection with the laboratory analysis may be compromised by computerization or automation, this information should be:

- provided with a written record of the program
- provided with appropriate written records of any associated validation data

Hardcopy or alternative systems, such as duplicates, tapes, or microfilm should be designed to assure backup data are exact and secure from alteration, inadvertent erasures, or other loss.

CFR 21 Sec 211.72 - Filters

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use should not release any fibers. If it is impossible to avoid use of a filter that releases fibers into the process, an additional non-fiber releasing filter of 0.22 micron maximum mean porosity (or 0.45 micron if the manufacturing process requires) should be subsequently used to reduce the content of particles in the injectable product.

Any asbestos-containing filters with or without the subsequent use of a specific non-fiber releasing filter should be used only with special permission of the FDA. For any asbestos-containing filter used, there must be documented proof sent to the appropriate bureau of the FDA that use of a non-fiber releasing filter will or is likely to compromise the safety or efficacy of the injectable product.

CFR 21 Sec 211.80

Written procedures should be kept and followed, describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug products, containers, and closures.

Bagged and boxed components of drug product containers or closures must be stored off the floor and suitably spaced to permit cleaning and inspection. Each container or grouping of containers for components, drug product containers, or closures should by properly identified with a distinctive code for each lot in each shipment received. The lot code used in recording the disposition of each lot should include appropriate identification as to its status (i.e. quarantined, approved, rejected, etc.)

CFR 21 Sec 211.84 - Testing and approval or rejection of components, drug product containers, and closures

Each lot of components, drug product containers, and closures should be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit. Representative samples of each shipment of each lot should be collected for testing or examination.

In sample planning, the number of containers to be sampled and the amount to be taken from each container should be based on appropriate criteria such as:

- statistical criteria for component variability
- confidence levels
- degree of precision desired
- past quality history of the supplier
- quantity needed for analysis including any applicable reserve where required by section 211.170

Samples should be collected as follows:

- selected containers are cleaned where necessary by appropriate means
- containers are opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures
- sterile equipment and aseptic sampling techniques are used where necessary
- sampling a container from the top, middle, and bottom (when necessary) is undertaken with care to ensure sample subdivisions are not composited for testing

Samples from containers should be identified to allow determination of the following information:

- name of the material sampled
- lot number
- container sample was taken from
- date on which the sample was taken
- name of the person collecting the sample

Containers from which samples have been taken should be marked to show that samples have been taken.

Samples should be examined and tested as follows:

- at least one test is conducted to verify the identity of each component of a drug product including specific identity tests (if they exist)
- each component should be tested for conformity with all appropriate written specifications for purity, strength, and quality

NOTE: In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component provided the following criteria is met:

- at least one specific identity test is conducted on the component by the manufacturer
- the suppliers report of analysis is validated by the manufacturer for reliability through appropriate validation of the supplier's test results at appropriate intervals
- containers and closures test for conformance with all written procedures

NOTE: In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier provided that the following criteria is met:

- a visual identification on such containers and closures is completed by the manufacturer
- the supplier's certificate of testing is validated by the manufacturer for reliability through appropriate validation of the supplier's test results at appropriate intervals, and components are microscopically examined when appropriate

CFR 21 Sec 211.86

FIFO: Components, drug product containers, and closures approved for use should be rotated so that the oldest approved stock is used first.

NOTE: Deviation from this requirement can be allowed but only if such deviation is temporary and appropriate.

CFR 21 Sec 211.87

Components, drug product containers and closures should be re-examined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with Sec 211.84 as necessary such as after long periods of storage or after exposure to heat, air, or other conditions that may adversely affect the copmonent, drug product container, or closure.

CFR 21 Sec 211.94

Drug product containers and closures must meet the following criteria:
- drug product containers and closures are non-reactive, additive, or absorptive so as to not alter the drug's safety, identity, strength, quality, or purity.
- closure systems provide adequate protection against foreseeable external factors in storage and use that could cause deterioration or contamination of the drug product
- drug product containers and closures are clean, and where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use
- written standards or specifications are in place, in addition to methods of testing and (where indicated) methods of cleaning, sterilizing, and processing to remove pyrogenic properties

CFR 21 Sec 211.100 - Written Procedures; Deviations

Written procedures for production and process control should be designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. These procedures should include all requirements below:

Written procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

Written production and process control procedures are followed and documented at the time of performance. Any deviations from the written procedures should be recorded and justified.

Written production and control procedures include the following criteria, which assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:
- the batch is formulated with the intent to provide not less than 100% of the labeled or established amount of active ingredient
- components for drug product manufacturing are weighed, measured, or subdivided as appropriate

- if a component is removed from the original container to another, the new container are identified with the following information:
    - component name or item code
    - receiving or control number
    - weight or measure in new container
    - batch for which component was dispensed, including product name, strength, and lot #
- weighing, measuring, or subdividing operations for components are adequately supervised

Each container of component dispensed to manufacturing should be examined by a second person to assure that:

- the component was released by the quality control unit
- the weight or measure is correct as stated in the batch production records
- the containers are properly identified

Each component added to the batch by one person should then be verified by a second person. If added by automated equipment, then it should likewise be verified by one person.

CFR 21 Sec 211.103 - Calculation of Yield

Actual yields and percentages of theoretical yield should be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. These yield calculations should be performed by one person and independently verified by a second person

CFR 21 Sec 211.105 - Equipment Identification

All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug should be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

Major equipment should be identified by a distinctive ID number or code that is recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product.

NOTE: In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

CFR 21 Sec 211.110 - Sampling and testing of in-process materials and drug products

To assure batch uniformity and integrity of drug products, written procedures should be established and followed to describe the in-process controls, tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.

Such control procedures should be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characterstics of in-process material and the drug product.

Such control procedures should include, but are not limited to the following (where appropriate):

- tablet or capsule weight variation
- disintegration time
- adequacy of mixing to assure uniformity and homogeneity
- dissolution time and rate
- clarity, completeness, or pH of solutions

There should be valid in-process specifications for such characteristics consistent with drug product final specifications and derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.

Examination and testing of samples should assure that the drug product and in-process materials conform to specifications.

Rejected in-process materials must be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

CFR 21 Sec 211.111 - Time Limitations on Production

When appropriate, time limits for the completion of each phase of production should be established to assure the quality of the drug product.

NOTE: Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

CFR 21 Sec 211.113 - Control of Microbiological Contamination

Appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile should be established and followed.

These processes should include validation of sterilization processes.

CFR 21 Sec 211.115 - Reprocessing

Written procedures should be established prescribing a system for reprocessing batches that do not conform to specifications, and the steps to be taken to ensure that reprocessed batches will conform with all established standards, specifications, and characteristics.

All reprocessing should be reviewed and approved by the quality control unit.

CFR 21 Sec 211.122 - Materials examination and usage criteria

Access to storage areas should be limited to authorized personnel. Obsolete and outdated labels, labeling, and other packaging materials should be destroyed.

The use of gang printing of labels for different drug products or different strengths or net contents of the same drug products is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

CFR 21 Sec 211.125 - Labeling Issuance

Strict control must be exercised over labeling issued for use in drug product labeling operations.

Labeling materials issued for a batch should be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

Procedures should be utilized to reconcile the quantities of labeling issued, used, and returned, and require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data.

Discrepancies should be investigated in accordance with Sec 211.192.

NOTE: Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with section 211.122(g)2.

Excess labeling bearing lot or control numbers should be destroyed. Returned labeling must be maintained and stored in a manner so as to prevent mix-ups and provide proper identification.

Procedures should be written with sufficient detail of the control procedures employed for label issuance, and are closely followed.

CFR 21 Sec 211.130 - Packaging and Labeling Operations

Written procedures should be in place and followed to assure that correct labels, labeling, and packaging materials are used for drug products.

These procedures should incorporate the following:
- prevention of mix-ups and cross-contamination by physical or spatial separation from operations on other drug products
- identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots

Note: Identification need not be applied to each individual container but must be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

- identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch
- examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record
- inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations

Inspection should also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed.

CFR 21 Sec 211.132 - Tamper-resistant Packaging Requirements for Over-the-Counter (OTC) Human Drug Products

The company should understand and comply with the following:

General: The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-resistant packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products.

Note: An OTC drug product (except a dermatological, dentifrice, insulin, or throat lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

The company must understand and comply with the following:

Each manufacturer and packer who packages an OTC drug product for retail sale shall package the product in a tamper-resistant package, if this product is accessible to the public while held for sale.

A tamper-resistant package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred.

To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design (e.g., an aerosol product container) or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture).

NOTE: For purposes of this section, the term "distinctive by design'' means the packaging cannot be duplicated with commonly available materials or through commonly available processes.

NOTE: For purposes of this section, the term "aerosol product'' means a product which depends upon the power of a liquefied or compressed gas to expel the contents from the container.

NOTE: A tamper-resistant package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity.

NOTE: The tamper- resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

CFR 21 Sec 211.132

The company must develop methods for compliance with the following as applicable:

- for two-piece, hard gelatin capsule products subject to this requirement, a minimum of two tamper-resistant packaging features is required, unless the capsules are sealed by a tamper- resistant technology
- for all other products subject to this requirement, including two-piece, hard gelatin capsules that are sealed by a tamper- resistant technology, a minimum of one tamper-resistant feature is required

Each retail package of an OTC drug product covered by this section requirement must bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package.

- the labeling statement should be placed so that it will be unaffected if the tamper-resistant feature of the package is breached or missing?
- if the tamper-resistant feature chosen to meet the requirement in this section is one that uses an identifying characteristic, that characteristic should be referred to in the labeling statement

NOTE: For example, the labeling statement on a bottle with a shrink band could say "For your protection, this bottle has an imprinted seal around the neck."

If the manufacturer or packer requested an exemption from the packaging and labeling requirements of this section, it must be formally submitted in the form of a citizen petition under § 10.30 of this chapter.

If the company has made any modifications or changes in packaging and labeling, the required approval from the FDA was achieved where necessary.

Prior FDA approval should be granted for any manufacturing changes by which capsules are to be sealed.

NOTE: Holders of approved new drug applications for OTC drug products are required under § 314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under § 314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under § 314.70(b) of this chapter.

CFR 21 Sec 211.134 - Drug Product Inspection

A representative sample of units should be collected at the completion of finishing operations and visually examined for correct labeling. The results of these examinations should be recorded in the batch production or control records.

CFR 21 Sec 211.137 - Expiration Dating

To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it must have an expiration date determined by appropriate stability testing described in section 211.166.

Expiration dates should be related to any storage conditions stated on the labeling, as determined by stability studies described in section 211.166.

If the drug product is to be reconstituted at the time of dispensing, its labeling should carry expiration information for both the reconstituted and non-reconstituted drug products.

Expiration dates should appear on labeling in accordance with the requirements of section 201.17 of Federal regulations

Exemptions exist for homeopathic drug products or allergenic extracts labeled “No U.S. Standard of Potency.”

NOTE: Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

CFR 21 Sec 211.150 - Distribution Procedures

Written procedures should be established, and followed, describing the distribution of drug products.

The written procedures should include:

- a procedure whereby the oldest approved stock of a drug product is distributed first

NOTE: Deviation from this requirement is permitted if such deviation is temporary and appropriate.

- a system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary

The laboratory controls should include:

- determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products

Procedures should require appropriate retesting of any component, drug product container, or closure that is subject to deterioration, with samples that are representative and adequately identified.

For the calibration of instruments, apparatus, gauges, and recording devices, a written program should be enacted containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met on file and implemented.

CFR 21 Sec 211.165 - Testing and Release for Distribution

For each batch of drug product, there must be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release.

NOTE: Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm must be established and documented. This validation and documentation should be accomplished in accordance with § 211.194(a)(2).

NOTE: Reprocessing may be performed.

Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

CFR 21 Sec 211.166 - Stability Testing

There should be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing should be used in determining appropriate storage conditions and expiration dates.

The written program must be followed and should include:
- sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability
- storage conditions for samples retained for testing
- reliable, meaningful, and specific test methods
- testing of the drug product in the same container-closure system as that in which the drug product is marketed
- testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted

An adequate number of batches of each drug product must be tested to determine an appropriate expiration date and a record of such data maintained.

NOTE: Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted.

Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, stability studies should be conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

For homeopathic drug products, these requirements must be followed:

- a written assessment of stability exists based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use
- evaluation of stability is based on the same container-closure system in which the drug product is being marketed
- allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section

CFR 21 Sec 211.167 - Special testing requirements

For each batch of drug product purporting to be sterile and/or pyrogen-free, there must be appropriate laboratory testing to determine conformance to such requirements, with the procedures in writing and adhered to.

For each batch of ophthalmic ointment, there must be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances, with the procedures in writing and adhered to.

For each batch of controlled-release dosage form, there must be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient, with the procedures in writing and adhered to.

CFR 21 Sec 211.170 - Reserve Samples

An appropriately-identified reserve sample that is representative of each lot in each shipment of each active ingredient should be retained. These reserve samples should consist of at least twice the quantity needed for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing.

The retention time should be as follows:

- for an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample should be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

- for an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, is the reserve sample shall be retained for:
  - three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less.

OR

  - six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.
- for an active ingredient in an OTC drug product that is exempt from bearing an expiration date under §211.137, the reserve sample should be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient

An appropriately-identified reserve sample that is representative of each lot or batch of drug product is retained and stored under conditions consistent with product labeling. The reserve sample should be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample should consist of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens.

Except for those drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches should be selected by acceptable statistical procedures and examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample.

Any evidence of reserve sample deterioration should be investigated in accordance with section 211.192. The results of examinations must be recorded and maintained with other stability data on the drug product.

NOTE: Reserve samples of compressed medical gases need not be retained.

The retention time for reserve samples is as follows:
- for a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample should be retained for 1 year after the expiration date of the drug product
- for a radioactive drug product, except for nonradioactive reagent kits, the reserve sample should be retained for:
  - three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less

OR

  - six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days

- for an OTC drug product that is exempt for bearing an expiration date under § 211.137, the reserve sample should be retained for 3 years after the lot or batch of drug product is distributed

CFR 21 Sec 211.173 - Laboratory Animals

Animals used in testing components, in-process materials, or drug products for compliance with established specifications must be maintained and controlled in a manner that assures their suitability for their intended use.

The company must be aware of and in compliance with the animal welfare act to include CFR Title 9 Chapter 1 subchapter A section 231 and 23, with all laboratory animals identified. Adequate records should be maintained showing the history of the laboratory animals' use.

CFR 21 Sec 211.176 - Penicillin Contamination

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product must be tested for the presence of penicillin.

It must be verified that such drug product is not to be marketed if detectable levels are found when tested according to procedures specified in `Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

CFR 21 Sec 211.180 - General Requirements (Records and Reports)

Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product should be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under section 211.137, 3 years after distribution of the batch.

Records should be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under section 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.

Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment should be readily available.

Written records required by this part should be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.

Written procedures established and followed for such evaluations and include provisions for:
- a review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch
- a review of complaints, recalls, returned or salvaged drug products, and investigations conducted under section 211.192 for each drug product

Procedures should be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under section 211.198, 211.204 or 211.208 of the Federal regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

CFR 21 Sec 211.182 - Equipment Cleaning and Use Log

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use should be included in individual equipment logs that show the date, time, product, and lot number of each batch processed.

The persons performing and double-checking the cleaning and maintenance must date and sign or initial the log indicating that the work was performed. Entries in the log should be in chronological order?

CFR 21 Sec 211.184 - Component, Drug Product Container, Closure, and Labeling Records

These records should include the following:
- the identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in section 211.80; and the date of receipt

NOTE: The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

- the results of any test or examination performed (including those performed as required by section 211.82 (a), section 211.84(d), or section 211.122(a)) and the conclusions derived
- an individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record must contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.

CFR 21 211.186 - Master Production and Control Records

To assure uniformity from batch to batch, master production and control records for each drug product are kept, including each batch size thereof, prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person.

Is the preparation of master production and control records described in a written procedure and such written procedure shall be followed?

The master production and control records should include:

- the name and strength of the product and a description of the dosage form
- the name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit
- a complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic
- an accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component?

NOTE: Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records.

- a statement concerning any calculated excess of component
- a statement of theoretical weight or measure at appropriate phases of processing?
- a statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to section 211.192 is required?
- a description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling?
- complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed?

CFR 21 Sec 211.188 - Batch Production and Control Records

Batch production and control records should be prepared for each batch of drug product produced and include complete information relating to the production and control of each batch. These records should include:

- an accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed
- documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:
  - weights and measures of components used in the course of processing
  - in-process and laboratory control results
  - inspection of the packaging and labeling area before and after use
  - a statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing
  - complete labeling control records, including specimens or copies of all labeling used
  - description of drug product containers and closures
  - any sampling performed
  - identification of the persons performing and directly supervising or checking each significant step in the operation
  - any investigation made according to section 211.192
  - results of examinations made in accordance with section 211.134

CFR 21 Sec 211.192 - Production Record Review

All drug product production and control records, including those for packaging and labeling, must be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications should be thoroughly investigated, whether or not the batch has already been distributed.

The investigation should extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

A written record of the investigation should be made to include the conclusions and follow-up.

CFR 21 Sec 211.194 - Laboratory Records

Laboratory records should include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

- a description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing
- a statement of each method used in the testing of the sample. The statement should indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested

NOTE: If the method employed is in the current revision of the United State Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.

NOTE: Copies may be obtained from: Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201-3301.

The suitability of all testing methods used must be verified under actual conditions of use.

- a statement of the weight or measure of the sample used for each test, where appropriate
- a complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product and lot tested
- a record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors
- a statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested
- the initials or signature of the person who performs each test and the date(s) the tests were performed
- the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards

Complete records should be maintained of any modification of an established method employed in testing. Such records must include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

Complete records should be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

Complete records should be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.

Complete records should be maintained of all stability testing performed.

CFR 21 Sec 211.196 - Distribution Records

Distribution records should contain the name and strength of the product and a description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

NOTE: For compressed medical gas products, distribution records are not required to contain lot or control numbers.

CFR 21 Sec 211.198 - Complaint Files

Such procedures should include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with section 211.192 to see if the complaint affects other batches.

Such procedures should include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with section 310.305 and 514.80 of the Federal regulations.

A written record of each complaint should be maintained in a file designated for drug product complaints.

Written records involving a drug product should be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer.

In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under section 211.137, such written records should be maintained for 3 years after distribution of the drug product.

The written record should include the following information, where known:
- the name and strength of the drug product, lot number, name of complainant, nature of the complaint, and reply to the complainant

Where an investigation under section 211.192 is conducted, the written record should include the findings of the investigation and the follow-up. The record or copy of the record of the investigation should be maintained at the establishment where the investigation occurred in accordance with section 211.180(c).

Where an investigation under section 211.192 is not conducted, the written record should include the reason that an investigation was found not to be necessary and the name of the responsible person for making such a determination.

CFR 21 Sec 211.208 - Drug Product Salvaging

Drug products that have been subjected to improper storage conditions (including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures) may or may not be salvaged or returned to the marketplace.

Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations should only be conducted if there is:
- evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity

AND
- evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident

NOTE: Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity.

Records including name, lot number, and disposition should be maintained for drug products subject to this section.

CFR 21 (Various) - Experimental Products and Materials (such as R&D)

There should be a written procedure in place for control of any experimental materials being used.

Such a procedure should describe and ensure the following:

- proper identification of any experimental products and materials
- any experimental products and materials should be properly segregated from normal production
- handling and control protocols should be properly described including shelf life of any products and materials
- proper management authorization and product development authorization should be recorded
- proper documentation must be made available regarding the scope of the use of such experimental products and materials
- experimental product and material release protocols must be properly described and recorded
- product and process validation for use of such experimental materials should be conducted with records being maintained of results

CFR 21 (Various) - Internal Audit

Written internal audit procedures should be established, including procedures to ensure that deficiencies identified are properly addressed in a timely fashion

There should be a written procedure for the scheduling and conducting of internal audits, and these audits should be conducted as planned. Internal audits must cover the requirements of 21 CFR 21o and 21 CFR 211. Audits should be performed in accordance with the written procedure, with audit results documented and recorded, as well as reviewed by management.

As appropriate, action should be taken to correct any deficiencies found in internal audits, with records maintained of these actions. All corrective actions should be undertaken in a timely manner. Actions taken must be effective to eliminate the root cause of the problem.

Internal auditors independent of the area being audited should be properly trained on audit techniques and the requirements of 21 CFR 210 and 21 CFR 211.