FDA's Guidelines for GMP of API

WITH DALTON

Peter Pekos

[COMPANY VISION]

"To make the impossible possible. Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

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- Contract Research
- Custom Synthesis
- Medicinal and Flow Chemistry
- API Process Development Formulation
- Development
- cGMP API Manufacturing
- cGMP Sterile Filling
- Analytical and Microbiology Services

FDA inspected, HC approved, & MRA with EMA

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ABOUT

Legislative Framework

Disclaimer

This technical report is intended to provide information to quality and regulatory correspondents on FDA's guidelines for the good manufacturing practices of active pharmaceutical ingredients. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

Act, Regulation, Gudielines

Act

An Act is a means by which laws are made that:

- Provide clarity on the definition and interpretation of the legal framework
- Establish actions that are prohibited
- Establish actions that are permitted
- Set out a framework for a regulatory scheme

Regulations

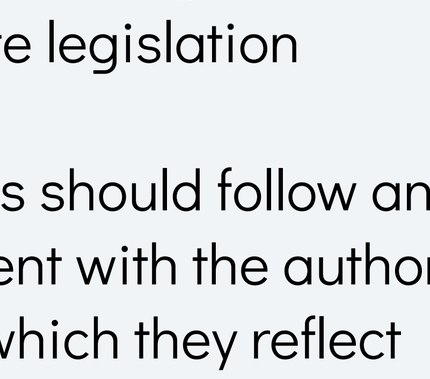
Regulations are the operational part of the law, that interprets what is meant by the terms, provisions, procedures, and processes in the Act in order to comply with the Act

Regulations are often referred to as delegated legislation or subordinate legislation

Regulations should follow and be consistent with the authority of the Act which they reflect (Enabling Act)

Guidelines

Guidance documents provide assistance on how to comply with laws and regulations. They serve as an administrative instrument and are not enforced by law



APIs are subject to the adulteration provisions of 21 USC 501(a)(2)(B), which requires all drugs to be manufactured in conformance with cGMP.

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ABOUT

API & GMP

API

An active pharmaceutical ingredient is defined as a

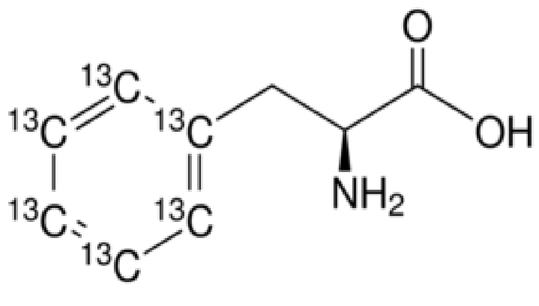
“(A) substance, or a mixture when the substance is unstable or cannot be transported on its own, intended

- (i) to be used as a component of a drug; and
- (ii) 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 human body; or

(B) substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture described in subparagraph (A)” (FDA, 2016).

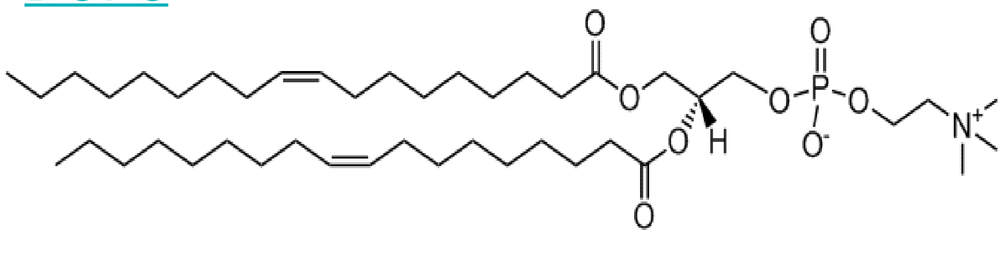
Once the API form is determined, the dosage form must be selected. To learn more about dosage form development refer to Dalton’s API and dosage form development technical report.

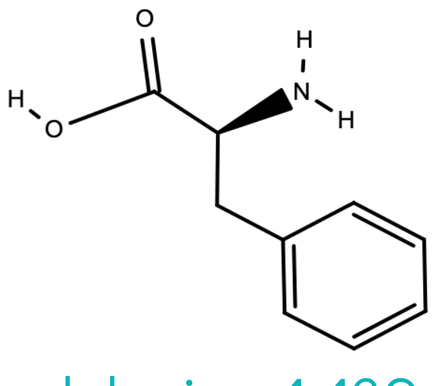
The quality of the API in a drug has a direct effect on the safety and efficacy of that drug. Therefore, GMP is a critical part of API development.



L-Phenylalanine, Ring-13C6

DOPC





L-Phenylalanine, 1-13C

GMP

Good Manufacturing Practices (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards, as required by the market authorization license.
Therefore, GMP serves to protect the health of the public.

Current Good Manufacturing Practices (cGMP) refers to the continuously evolving GMPs of drug development. Dalton’s 15 years of expertise in complex cGMP APIs can support your clinical development through to commercialization.

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Quality by Design

"Quality After Design" involves increased testing after product production. This approach was the mainstay by drug manufacturing companies up until the 1990s. In the 1990s FDA recognized that increased testing does not necessarily improve product quality but rather building quality into a product does.

The notion of building quality into a product to improve product quality became known as Quality by Design (QbD).

QbD involves having an understanding of:

- The product
- The process by which it is developed and manufactured along with
- The risks involved with manufacturing
- How to best mitigate those risks

Risk management involves establishing a risk management framework by defining the process, roles, and responsibilities and creating a risk management plan.

Risk Management Plan

Refer to ICHQ9 for more information on quality risk management.

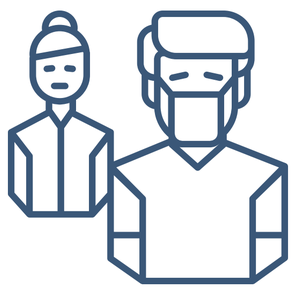
ABOUT

Regulations

eCFR Title 21, Part 210-211

The FDA has not implemented regulations specifically for cGMP of APIs. However, Title 21, Parts 210 - 211 apply to APIs.

Part 210 states that the cGMPs outlined in part 211 are appliable to the manufacture, processing, packing, or holding of a drug. Note: The production of an investigational drug for use in a phase 1 study is exempt from compliance with the regulations in part 211. The cGMP requirements outlined in Part 211 are:

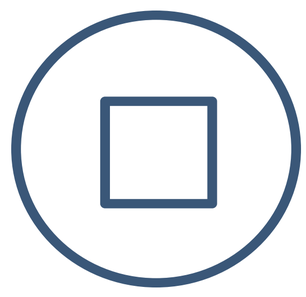


Organization and Personnel

- Responsibilities of quality control unit
- Personnel qualifications
- Personnel responsibilities
- Consultants

Laboratory Controls

- Testing and release for distribution
- Stability testing
- Special testing requirements
- Reserve samples
- Laboratory animals
- Penicillin contamination



Holding and Distribution

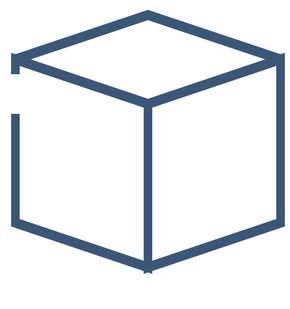
- Warehousing procedures
- Distribution procedures

Buildings and Facilities

- Design and construction features
- Lighting
- Ventilation, air filtration, air heating and cooling
- Plumbing
- Sewage and refuse
- Washing and toilet facilities
- Sanitation
- Maintenance

Equipment

- Equipment design, size, and location
- Equipment construction
- Equipment cleaning and maintenance
- Automatic, mechanical, and electronic equipment
- Filter



Packaging and Labeling Control

- Materials examination and usage criteria
- Labeling issuance
- Packaging and labeling operations
- Tamper-evident packaging requirements for over the counter (OTC) human drug products
- Drug product inspection
- Expiration dating

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Regulations

Control of Components and Drug Product Containers and Closures

- Receipt and storage of untested components, drug product containers, and closures
- Testing and approval or rejection of components, drug product containers, and closures
- Use of approved components, drug product containers, and closures
- Retesting of approved components, drug product containers, and closures
- Rejected components, drug product containers, and closures
- Drug product containers and closures

Production and Process Controls

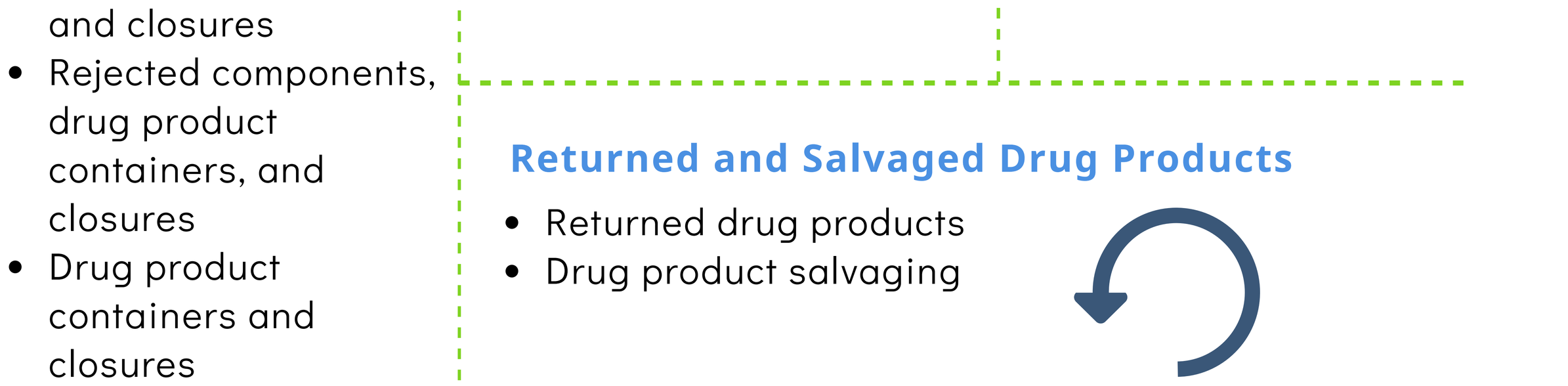
- Written procedures; deviations
- Charge-in of components
- Calculation of yield-
- Equipment identification
- Sampling and testing of in-process materials and drug products
- Time limitations on production
- Control of microbiological contamination
- Reprocessing

Records and Reports

- Equipment cleaning and use log
- Component, drug product container, closure, and labeling records
- Master production and control records
- Batch production and control records
- Production record review
- Laboratory records
- Distribution records
- Complaint files

Returned and Salvaged Drug Products

- Returned drug products
- Drug product salvaging



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Guidelines

Q7 GMP for API Guideline

The guidance document “Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry” represents FDA’s current thinking of GMPs for the production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and replaces the guidance document “Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.”

Out of scope: vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), gene therapy, medical gases, bulk-packaged drug (medicinal) products (e.g., tablets or capsules in bulk containers), and radiopharmaceuticals APIs.

The stringency of GMPs in API manufacturing gradually increases as it gets closer to the final steps.

Quality Management

- The Quality Control Unit is responsible for
  - All activities (e.g., tests) and decisions concerning the quality of the product
  - Releasing or rejecting APIs
  - Establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials

  The Quality Assurance Unit is responsible for
- - Reviewing and approving all quality-related documents
  - Ensuring compliance to GMPs
  - Ensuring self-inspection audits are performed
  - Analyzing quality non-conformance issues and suggesting corrective and preventive actions (CAPA)
- Internal audits - Ensure investigation and CAPA for critical deviations and complaints
- Product quality review - A product quality review that includes trend analysis is expected annually

Personnel

- Personnel qualifications - Personnel must have education, training that is periodically assessed, and experience
- Personal hygiene - Personnel should avoid direct contact with APIs
- Consultants - If a consultant is used, they must be qualified by education, regular training, and experience

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Buildings and Facilities

- Design and Construction
  - Must be designed and constructed to facilitate cleaning, maintenance, and operations and it must be located in a space that permits orderly placement of equipment and material
  - Have defined areas for the following:
    - Receipt, identification, sampling, and quarantine of incoming materials,
    - Sampling,
    - Holding,
    - Storage of released materials,
    - Production operations,
    - Packaging and labeling operations, and
    - Laboratory operations
  - Toilet facilities should be equipped with hot and cold water
- Utilities - Must have adequate ventilation, air filtration, and exhaust systems
- Water
  - Water used in the manufacture of an API should be demonstrated to be suitable for its intended use
  - Water treatments must be validated and monitored with appropriate action limits
- Containment - Employ dedicated production areas for highly sensitizing materials (e.g., materials such as penicillins and cephalosporins)
- Lighting - Must have adequate lighting
- Sewage and Refuse - Must be disposed of in a safe, timely, and sanitary manner
- Sanitation and Maintenance

Process Equipment

- Design and construction
  - Must have an appropriate design and adequate size. Locate in a space that permits for its intended use, cleaning, sanitization, and maintenance
  - Only use production equipment in its qualified operating range
  - Equipment processing aids should not contact APIs
- Equipment Maintenance & Cleaning
  - Establish schedules and procedures for the preventative maintenance of equipment
  - Inspect equipment for cleanliness before use
  - Establish schedules and procedures for the cleaning of equipment
  - Keep a record of the methods and materials used to clean equipment
- Calibration
  - Establish a schedule and written procedures for the calibration of equipment used to control, weigh, measure, monitor, and test APIs. Base calibrations on certified standards and document this
  - Do not use equipment that does not meet calibration acceptance standards
- Computerized Systems
  - Validate GMP related computerized systems
  - Have sufficient controls to prevent unauthorized access and to verify the input of critical data
  - Establish written procedures for its operation
  - Have a backup system

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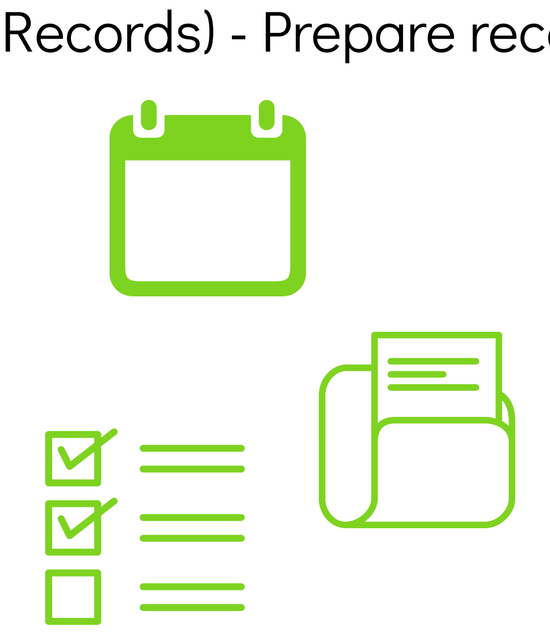
Documentation and Records

- Documentation System and Specifications
  - Prepare, review, approve, and distribute API manufacturing documents per written procedures
  - Retain all production, control, and distribution records for at least 1 year after the complete distribution of the entire batch of the API by the API manufacturer to the next party in the supply chain. The records should be in their original form. For APIs with a retest date, retain records for at least 3 years after the batch is completely distributed.
  - Records must provide the name of the personnel that entered any information
- Equipment Cleaning and Use Record - Record the date, time, product, and batch number of cleaning, sanitization, sterilization, and maintenance of all major equipment's
- Records of Raw Materials, Intermediates, API Labeling, and Packaging Materials - Records should include
  - The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s); the number allocated on receipt; and the date of receipt
  - Results on tests
- Master Production Instructions (Master Production and Control Records)
  - Prepare a master production instruction for the API. This should include the API name, the identifying document reference code, a list of raw materials with their quality characteristics and quantity, the production location, production equipment, production instruction, and API storage. This should be reviewed, dated, and signed by the QA Unit.
- Batch Production Records (Batch Production and Control Records) - Prepare records for API batch production that includes the:
  - Date and time,
  - Major equipment used,
  - Batch description (e.g., number, weight),
  - Sampling performed,
  - Laboratory test results,
  - Packaging and labeling information, and
  - Deviations and evaluations



- Laboratory Control Records
  - Record a description of samples received for testing. This description should include material name, batch number, and quantity
  - Date the sample was received for testing and date it was sampled
  - Reference to each test method
  - Weight of sample used for each test
  - Record of all raw data
  - Signature of the personnel who performed each test and of the personnel who reviewed it
- Batch Production Record Review - Establish written procedures for the review and approval of batches

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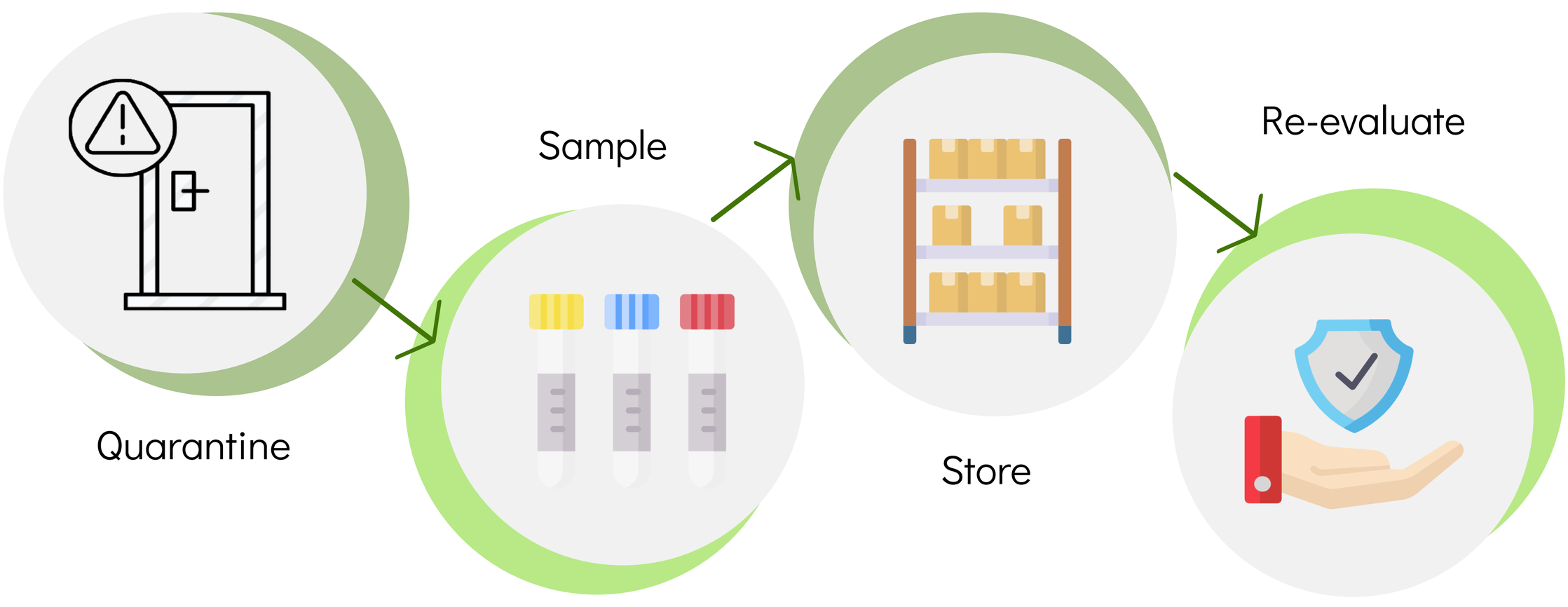
Material Management

- General Controls - Establish written procedures for the receipt, identification, quarantine, storage, handling, sampling, testing, approval or rejection, and supplier evaluation of materials
- Receipt and Quarantine
  - Visually examine each container of materials upon receipt and before acceptance
  - Quarantine material until sampling, examination, or testing, has been conducted
- Sampling and Testing of Incoming Production Materials
  - Test incoming material to verify the identity of each batch
  - A supplier's certificate of analysis can be used in place of performing a test
- Storage - Store and handle material in a way that prevents degradation, contamination, and adverse effect on its quality
- Re-evaluation - Re-evaluate materials to determine if they are still suitable for use (e.g., after prolonged storage or exposure to heat or humidity)



Production and Inprocess Controls

- Production Operations
  - Weigh or measure API in a way that does not affect its suitability for use. Activities should be witnessed or subjected to an equivalent control
  - Compare actual yields with expected yields. Explain and document any deviations; investigate if necessary
- Time Limits - Meet the time limits in the master production instruction
- In-process Sampling and Controls - Establish written procedures
- Blending Batches of Intermediates or APIs
  - Do not blend out-of-specification batches with other batches
  - Acceptable blending operations:
    - Blending of small batches to increase the batch size
    - Blending tailings from batches of the same API to form a single batch
  - Control, test, and document any blending processes
- Contamination Control - If there is adequate control, residual materials can be carried over into successive batches of the same API

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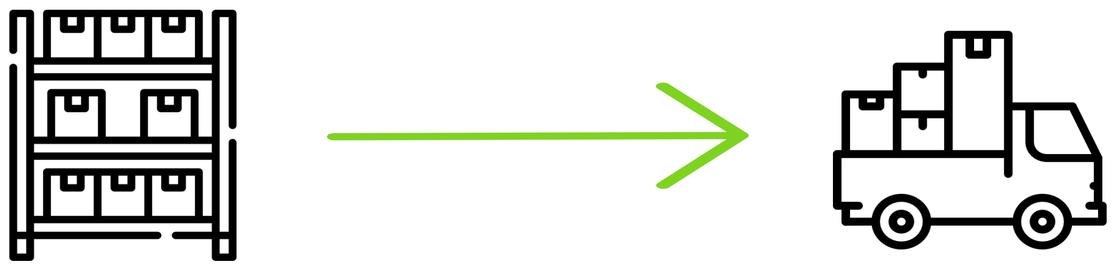
Packaging and Identification Labeling of API

- General
  - Establish written procedures for the receipt, identification, quarantine, sampling, examination/testing, release, and handling of packaging and labeling materials
  - Maintain records for each shipment of labels and packaging materials showing the receipt, examination, or testing, and an indication on whether it was accepted or rejected
- Packaging Materials - Packaging material containers should provide adequate protection against deterioration or contamination
- Label Issuance and Control
  - Limit access to authorized personnel
  - Destroy out-dated labels
- Packaging and Labeling Operations

Storage and Distribution

- Warehousing Procedures - Facilities should have available storage area with conditions that can be altered (e.g., controlled temperature and humidity when necessary)
- Distribution Procedures
  - Release APIs for distribution to third parties only if it has been released by the quality unit
  - Transportation of APIs must not affect its quality



Laboratory Controls

- Testing of Intermediates and APIs - Establish an impurity profile for a typical batch produced by a specific controlled production process
- Validation of Analytical Procedures
- Certificates of Analysis - Authentic Certificates of Analysis should be issued for each API batch on request
- Stability Monitoring of API - An ongoing testing program should be designed to monitor the stability characteristics of an API, and the results should be used to confirm appropriate storage conditions and retest or expiry dates
- Expiry and Retest Dating
  - An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date
  - The retest date can be extended based on good science and long-term stability results and if the batch has been stored correctly
- Reserve/Retention Samples - Retain API batch samples in the case of future quality evaluation. Serves as a legal basis since retention samples permit for a thorough and effective investigation for complaint handling

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Guidelines

Validation

- Validation Policy - Document the company's overall policy, intentions, approach to validation, validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase.
- Qualification - Document verification of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ)
- Process Validation
  - Types of process validation
    1) Prospective validation: Perform for all API processes before the commercial distribution of the final drug product manufactured from that API
    2) Concurrent Validation: A subset of prospective validation that is conducted to ultimately distribute product manufactured during the validation study and which becomes the In Process Quality Control Tests (I.P.Q.C) tests
    3) Retrospective Validation: Confirms the impurity specifications for each API
  - Periodic Review of Validated Systems
  - Cleaning Validation - Validations should reflect the actual process carried out during equipment cleaning
  - Validation of Analytical Methods - Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process

Complaints and Recalls

- Manufacturers, importers and distributors are obligated to maintain records of reported problems and all actions taken in response to these problems
- Manufacturers, importers and distributors are also obligated to establish and implement documented procedures for effective and timely investigation/ response
  - Complaint handling procedure: Identify activities that must take place, identify personnel involved and their role, identify how to maintain and access records, identify timeframes for completion of investigations
  - Failure to do so results in penalties, including imprisonment
- Record and investigate the following information
  - Name and address of the complainant
  - Name and phone number of the person submitting the complaint
  - Complaint nature (including name and batch number of the API)
  - Awareness Date
  - CAPA
  - Response provided to the originator of complaint (including date the response was sent)
  - Decision on API batch or lot
- Adverse drug reaction report
  - MedWatch (FDA 3500a) for adverse drug reactions in the US
  - CIOMS for adverse drug reactions outside the US

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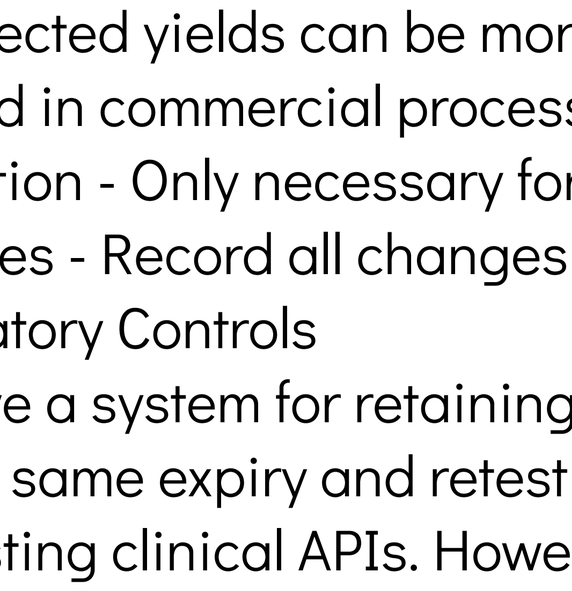
Guidelines

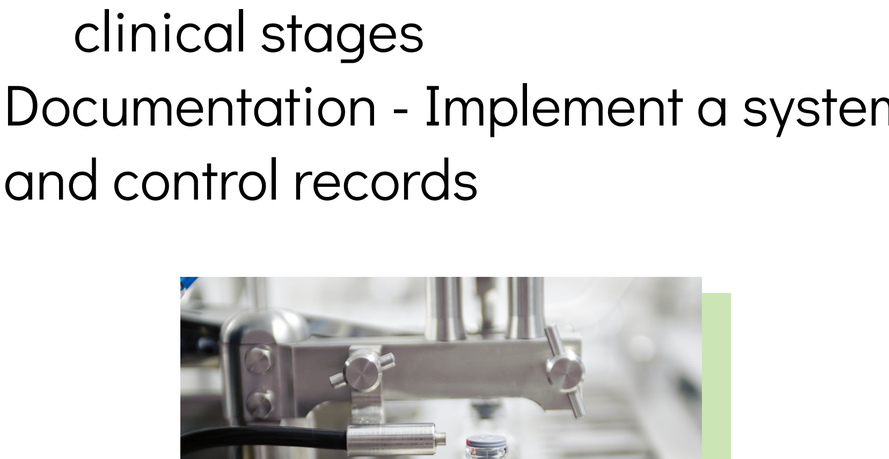
Rejection and Reuse of Materials

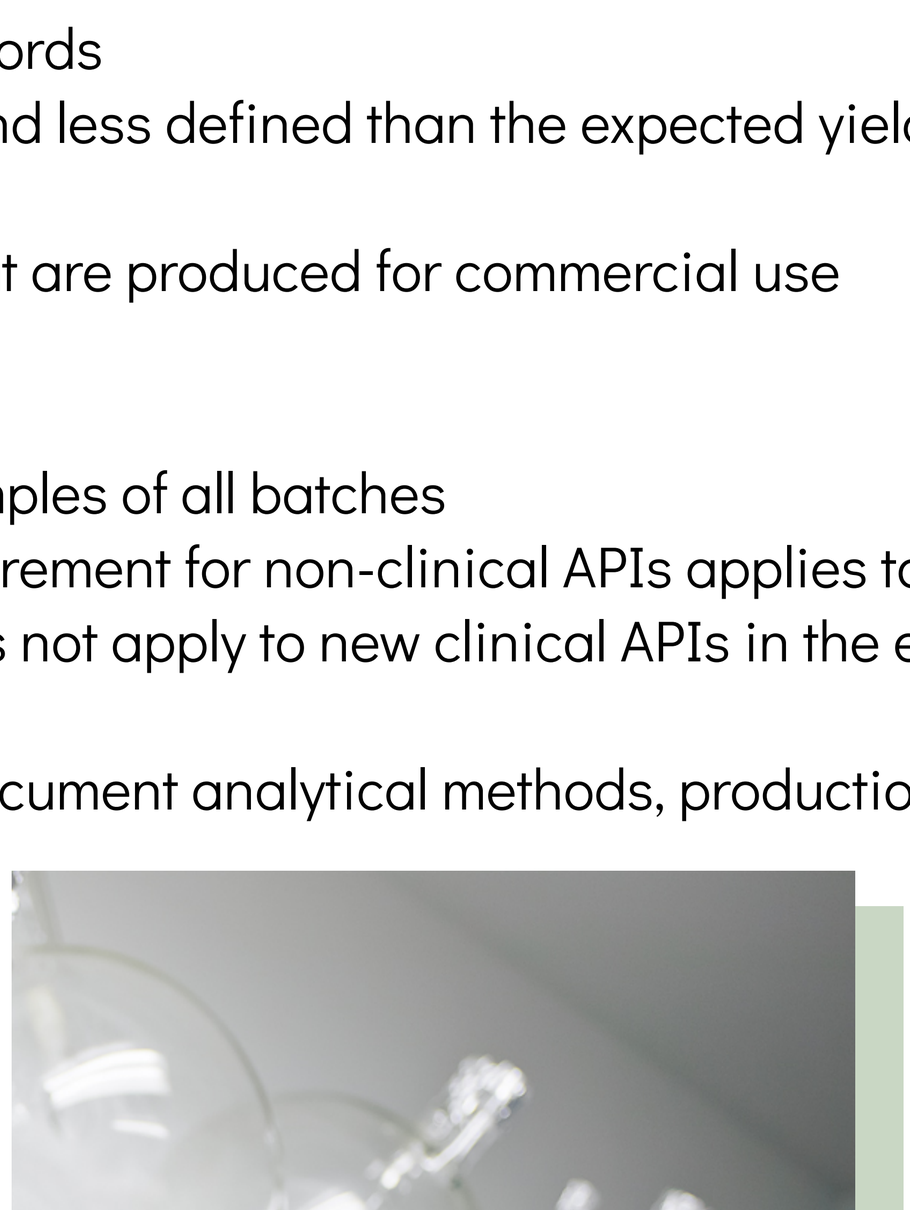
- Rejection and Reuse of Materials
  - Rejection
  - Reprocessing
  - Reworking
  - Recovery of materials and solvents
  - Returns

APIs for Use in Clinical Trials

- Quality
  - Apply GMPs
  - Establish quality unit(s) independent, from production, for the approval or rejection of each batch of API
- Equipment and Facilities
  - During all phases, equipment should be calibrated, clean, and suitable
  - It is permitted to use the same equipment to manufacture materials in both preclinical and clinical trials
- Control of Raw Materials - Evaluate by testing
- Production
  - Document in lab notebooks or batch records
  - Expected yields can be more variable and less defined than the expected yields used in commercial processes
- Validation - Only necessary for batches that are produced for commercial use
- Changes - Record all changes
- Laboratory Controls
  - Have a system for retaining reserve samples of all batches
  - The same expiry and retest dating requirement for non-clinical APIs applies to existing clinical APIs. However, this does not apply to new clinical APIs in the early clinical stages
- Documentation - Implement a system to document analytical methods, production, and control records







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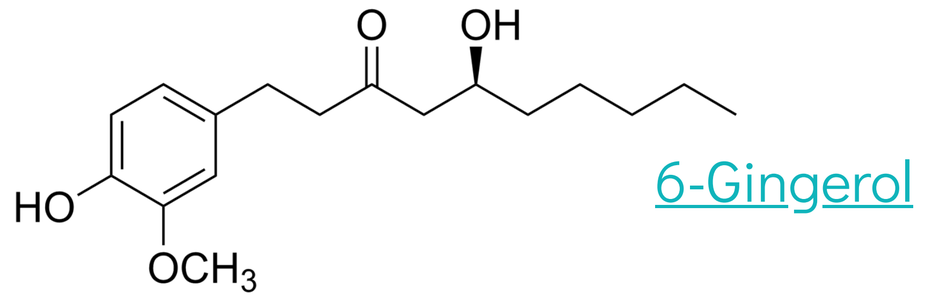
Dalton's Services

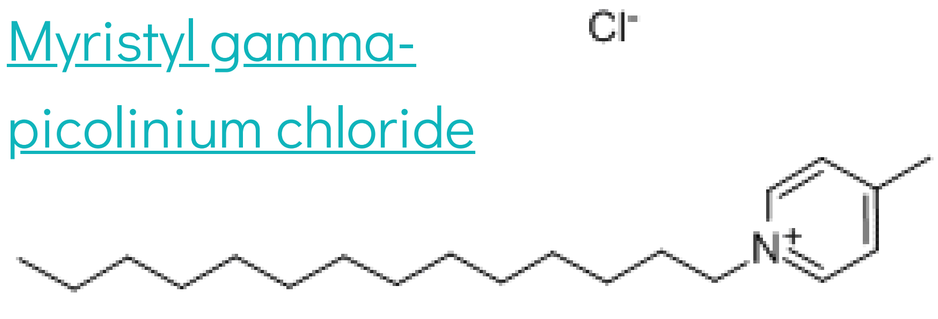
cGMP API Manufacturing

Dalton is a leader in the development and manufacture of complex cGMP Active Pharmaceutical Ingredients (APIs). Our expert scientists, coupled with newly updated and renovated cGMP development and manufacturing facility allow us to support API Synthesis. We conduct cGMP manufacturing of APIs for all stages of pre-clinical and clinical trials, from grams to multi-kilos.



6-Gingerol

Myristyl gamma-picolinium chloride



We pay special attention to equipment qualification and process validation and provide full regulatory support for our clients. Dalton can develop, create, and execute validation protocols and studies required for your products and equipment in accordance with current regulations and guidelines (U.S. FDA, Health Canada, EMA, ICH, and WHO) and acceptable formats (prospective, retrospective, and concurrent).

Learn more about our API Manufacturing capabilities here.

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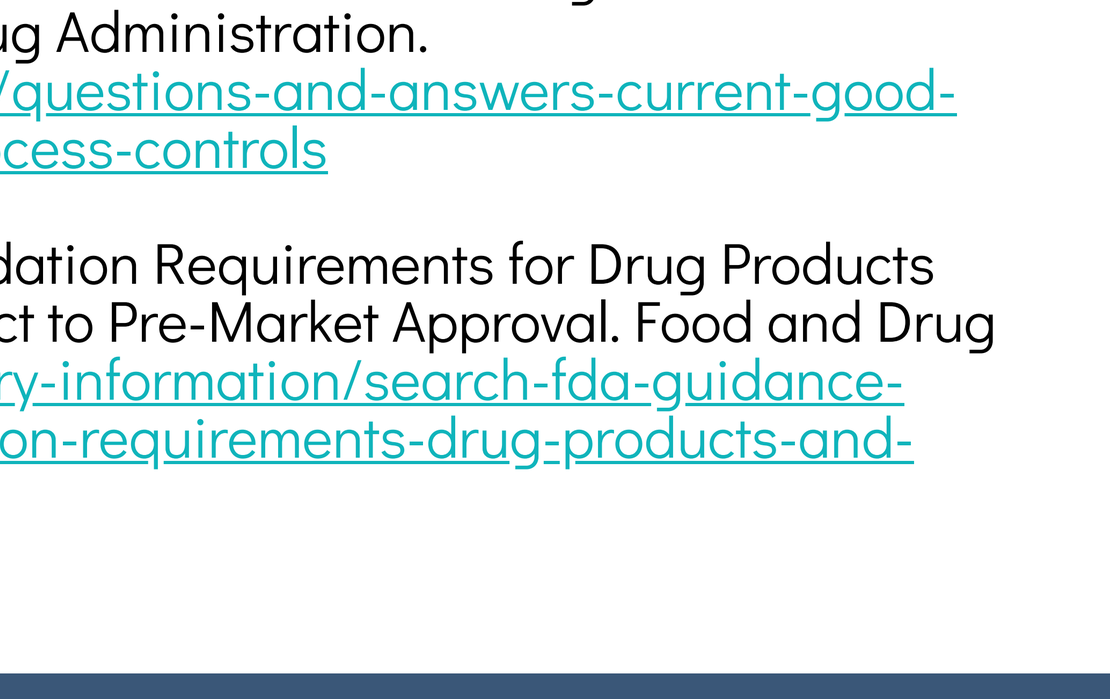

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