Canadian Guidelines for GMP of API

WITH DALTON

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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."

Services

- 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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Pharmaceutical Drugs

Disclaimer

- In scope: pharmaceutical APIs
- Out of scope: bulk process intermediates (BPI), biologics, radiopharmaceutical, medical devices, NHP, veterinary drugs

Pharmaceutical Drugs

- Manufactured by chemical synthesis
- Elicits therapeutic effects through chemical means
- Sold within Canada as a prescription or over the counter. Note that sterile pharmaceuticals are only sold through prescription
- Stored/manufactured at ambient room temperature
- Can be a solid dose form (e.g., capsules) or an injectable form (e.g., intravenous). The solid form comes in hermetically controlled packages and the injectable form comes in sterile form
- Dalton can help you to determine the optimal dosage form for your API. Form selection in API depends on your API's solubility and dissolution, excipient compatibility, solid state analysis, and stability. Formulations we offer:
  - Oral Immediate Release & Controlled Release
  - Topical and Transdermals
  - Sterile Liquids
  - Powders
  - Sterile Liquid Dosage Formulations
  - Injectable Drugs
  - Lyophilized Formulations

World Health Organization (WHO) defines Good Manufacturing Practices (GMP) as "a system for ensuring that products are consistently produced and controlled according to quality standards." Past tragic incidents such as the thalidomide pandemic and the Cutter incident led to the recognition of the importance of GMP.

GMP is governed under Part C DIVISION 2 (C.02.001) of the Food and Drug Regulations. GMP for active pharmaceutical ingredients (API) addresses all areas that affect process performance and product quality, including:

Premises	Quality control
Equipment	Packaging material testing
Personnel	Finished product testing
Sanitation	Records
Raw material testing	Samples
Manufacturing control	Stability

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GMP for API

1 Premises *enabling regulation: C.02.004*

- Allow for cleanliness, maintenance, and contamination prevention.
- Have defined areas for specific activities, such as quarantine of APIs.
- Separate laboratory areas/operations from production areas in cases where the production process may impact the accuracy of the laboratory measurements.
- Highly toxic non-pharmaceutical materials should not be conducted in the same building or with the same equipment used for the production of APIs.
- Establishments must be suitable for their intended purpose with proper lighting, air handling, plumbing, sanitation, and adequate space for orderliness.

2 Personnel *enabling regulation: C.02.006*

- A sufficient number of personnel must be qualified. Qualified personnel are individuals with technical, academic, and GMP training.
- Clear roles and responsibilities need to be written and followed. This includes training before a new SOP is implemented or revised.
- Training methods need to be reviewed, maintained, and documented.
- NOTE: a company is not required to notify Health Canada of a change in key personnel.

3 Equipment *enabling regulation: C.02.005*

- Equipment should permit for cleaning, sanitization, and maintenance to prevent cross-contamination.
- Place in a location that is suitable based on its intended use.
- Construct equipment in a way that prohibits the alteration of material when it comes to contact with its surface.
- Equipment such as ovens and autoclaves must contain only one API at a time with the exception that precautions are taken to prevent contamination and mix-ups.
- Equipment calibrations should be performed.

4 Sanitation *enabling regulation: C.02.007 – C.02.008*

- A written sanitation program must be implemented by qualified personnel. This includes written procedures for cleaning and for the use of suitable pesticide agents.
- An environmental monitoring program must also be implemented.
- Records of cleaning, sanitization, and sterilization should be maintained.
- Acceptance criteria for residues should be defined and justified.
- Personnel and visitors should practice good sanitation and health habits.
- Access to drug fabrication or packaging/labelling areas by personnel that have an open lesion, or a communicable disease must be prohibited.

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GMP for API cont'd

5 Raw Material Testing *enabling regulation: C.02.009 – C.02.010*

- Specifications and acceptance criteria should be approved, established, and documented for starting materials, intermediates, bulk products, finished products, and primary packaging materials
- Written procedures describing the identification and testing of materials should be implemented.
- Process water should be demonstrated to be suitable and in accordance with WHO guidelines for water quality.
- For each batch recieved on the premises, conduct specific identity testing of the API fabricator.
- Any changes related to critical raw materials must be documented through a change control system (i.e., TrackWise).
- Transportation and storage conditions should not alter the potency, purity, or physical characteristics of the critical raw materials.

6 Manufacturing Control *enabling regulation: C.02.011 – C.02.012*

- A written validation protocol should be established
- Any deviation should be documented and explained.
- Actual yields should be compared with expected yields.
- This section also contains regulations for manufacturing operations, blending, recovery, packaging operations, and product quality review.

7 Quality Control *enabling regulation: C.02.013 – C.02.015*

- The quality unit of the fabricator and packager/labeller should be separate from production and fulfill the responsibilities of quality assurance and quality control.
- This section also contains regulations for reworking and reprocessing.

8 Other Regulations

- Packaging material testing (enabling regulation: C.02.016 – C.02.017)
- Finished product testing (enabling regulation: C.02.018 – C.02.019)
- Records (enabling regulation: C.02.020 – C.02.024)
- Samples (enabling regulation: C.02.025 – C.02.026)
- Stability (enabling regulation: C.02.027 – C.02.28)
- Sterile products (enabling regulation: C.02.029)
  - Manufacturing sterile products is subject to special requirements, to minimize risks of microbiological contamination and particulate and pyrogen contamination. Sterile products must be fabricated and packaged/labelled:
    - “in separate and enclosed areas
    - under the supervision of personnel trained in microbiology
    - by a method scientifically proven to ensure sterility” (Health Canada, 2014)

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Annex to GMP for Sterile API

In scope: pharmaceuticals, radiopharmaceuticals, biologics, veterinary drugs

Manufacturing of sterile products is governed in Part C, Division 2, section C.02.029 of the Food and Drug Regulations.

Grades for the manufacture of sterile drugs:

- "Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow workstation. Unidirectional air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of uni-directional flow should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.
- Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.
- Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products" (Health Canada, 2014).

Most Important Additions

Clean room and clean air device classification

- The values for the maximum permitted particles have been changed. Classification of clean rooms and clean air devices should be in accordance with provisions in EN ISO 14644-1.
- The minimum amount of sampling points/volume and interpretation of results should also be in accordance with EN ISO 14644-1
- Particle counters with long tube lengths will no longer be acceptable for clean room classification.

Clean room / clean air device monitoring

- The frequency, location, and number of monitoring locations should be based on a formal risk assessment and not on ISO 14644-1.
- Continuous monitoring is expected in critical areas with exposed product.

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GMP for Sterile Manufacturing

The GMP requirements for personnel, premises, equipment, and sanitation for sterile API follow the same principles as the GMP requirements for non-sterile API. In addition, sterile products are also subject to the special requirements listed below:

Personnel

- PPE and clothing of personnel depends on the grade.
- Personnel involved in microorganisms of animal tissues other than those meant for the current manufacturing process should not enter sterile product areas.

Premises

- There should be no spaces that are not cleanable and there should be minimal projecting ledges, shelves, cupboards, and equipment.
- Sinks and drains should be prohibited in grade A/B areas for aseptic manufacture.
- A warning system should be provided to indicate failure in the air supply.

Equipment

- Unless a conveyor belt is continually sterilized, it should not pass between a grade A or B area or a processing area of lower air cleanliness.
- Ensure a reliable source of water for water treatment plants and distribution systems.
- Subject all equipment to validation and planned maintenance.

Sanitation

- Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.
- Fumigation of clean areas in inaccessible places is advisable.

Additional GMP Requirements for Sterile API

Isolator Technology

- Isolators are a technology that provide continuous isolation from the external environment.
- Design the isolator so that the required air quality for the respective zones can be realized.
- Introduce isolator only after appropriate validation.
- Monitoring of isolator should include leak testing.

Blow/Fill/Seal Technique

- Blow-fill-seal technology is an advanced aseptic technique used to continuously fill and seal liquid containers through an automated system.
- Install in a grade C environment if it is fitted with an effective grade A air shower and grade A/B clothing is used. At rest the environment should comply with the viable and non-viable particle limits. When in operation rest the environment should comply with the viable limit only.
- Install in a grade D environment if it is used for the production of products that are terminally sterilized.

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GMP for Sterile Manufacturing

Terminally Sterilized Products

- Terminally sterilized products are products that have been sterilized in their final container but are not yet sterilized by other means such as heat.
- Preparation of components and products should be performed at minimum in a grade D environment.
- If the product is at a high or unusual risk of microbial contamination preparation should be performed in a grade C environment.
- Filling of products for terminal sterilization should be carried out in at least a grade C environment.
- Where the product is at unusual risk of contamination from the environment, the filling should be done in a grade A zone with at least a grade C background.

Aseptic Preparation

- Handle washed components in at least a grade D environment.
- Handle sterile starting materials and components in a grade A environment with grade B background.
- Prepare solutions which are to be sterile filtered during the process in a grade C environment.
- Prepare solutions which are not to be sterile filtered during the process in a grade A environment with a grade B background.
- Handle aseptically prepared products in a grade A environment with a grade B background.
- Transfer partially closed containers, prior to stoppering completion, in a grade A environment with grade B background or in sealed transfer tray in a grade B environment.

Processing

- Always take precautions to minimize contamination.
- Processing of products with microbiological origin should be separated from other drugs.
- Aseptic processing should be validated. Use a process simulation test as a form of validation twice a year.
- Regularly monitor water sources and treatment equipment for contamination and endotoxins.
- The time interval between the washing and drying and the sterilization of components should be minimized.
- The time interval between the start of the preparation of a solution and its sterilization or filtration should be minimized.
- Any article required in a clean area where aseptic work takes place should be sterilized and passed into the area through double-ended sterilizers sealed into the wall.

Sterilization

- Validate sterilization processes and record this for each run.
- It is recommended to use biological indicators as an additional method for monitoring the sterilization.
- Products that are not sterilized should be clearly differentiated from products that are sterilized.

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GMP for Sterile Manufacturing

Sterilization by Heat

- Record each heat sterilization cycle on a time/temperature chart.
- It is recommended to use chemical or biological indicators as an additional method.

Sterilization with Ethylene Oxide

- Permitted only if no other method is practicable.
- Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process.
- Monitor each sterilization cycle with suitable biological indicators and record.

Moist Heat

- To monitor the process, temperature and pressure should be used.
- Items to be sterilized should be wrapped in a material that permits the removal of air and penetration of steam but prevents recontamination after sterilization. Products in sealed containers are the exception.
- The steam used for sterilization should not contain additives at levels that can cause contamination.

Dry Heat

- Air circulation within the chamber and maintenance of a positive pressure should be used.

Sterilization by Radiation

- Permitted only if data confirms the absence of deleterious effects on the product.
- Measurement of radiation dose should be done through dosimetry indicators. Biological indicators may also be used as an additional control.
- Administered within a predetermined time span.
- Handling procedures should prevent mix-up between irradiated and nonirradiated materials.

Filtration of Drugs

- Filtration of drugs which cannot be sterilized in their final container can be filtered through a sterile filter of nominal pore size. However, steam sterilization is preferred.
- Verify the integrity of sterilized filter before and immediately after use.
- Do not use the same filter for more than one day.

Finishing of Sterile Products

- Perform a 100% integrity testing on containers closed by fusion.
- Perform crimping of the aluminium cap immediately after stopper insertion.
- Crimping equipment must be in a separate station equipped with adequate air extraction.

ICH, Non-compliance, and CTD

ICH Guidance

- ICH Q7 Guideline: Section 18 - Specific Guidance for APIs Manufactured by Cell Culture/Fermentation
- ICH Q7 Guideline: Section 19 - APIs for Use in Clinical Trials

Non-compliance of GMP

Penalties for GMP non-compliance in Canada includes:

- Fines
- Losing licensing
- Loss of reputation due to public exposure

  HC non-compliant inspections and drug recalls are easily accessible to the public through the drug and health products inspections database (DHPID). DHPID provides information on the company's address and details of observations, jeopardizing public relations.

CTD and GMP

A Common Technical Document (CTD) is a common format in many jurisdictions (including Health Canada) for the regulatory filing of Chemistry Manufacturing and Control (CMC) information.

CMC contains information regarding Part C – Drugs –Division 2 GMP:

- Facility and establishment information
- Premises, equipment, personnel, sanitation, storage
- Manufacturing procedures and controls
- Raw materials
- Packaging components
- Records
- Stability

The CTD is composed of 5 modules. Module 1 is region specific, module 2, 3, 4, and 5 are intended to be common for all regions.

Note: An establishment licence also requires CMC information.

Dalton's Services

With over 15 years of experience in sterile API, Dalton can support your GMP sterile manufacturing and filling needs for clinical development to commercialization.

Dalton offers GMP for sterile API manufacturing through a variety of methods including sterile filtration and dry heat sterilization. We can also help you determine the optimal dosage form for your API.

Learn more about our cGMP sterile manufacturing and fill/finish capabilities.

- Aseptic Vial Filling - Sterile Liquid Injectables
- Lyophilization Services
- Sterile Lyophilized Vials
- Sterile Powder Filling in Vials
- Steriles Made Simple SM

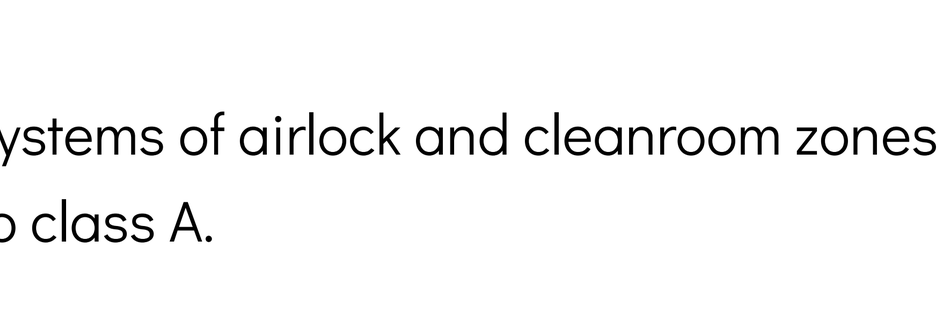
Our site has systems of airlock and cleanroom zones from class D to class A.

For a full list of our services visit www.dalton.com

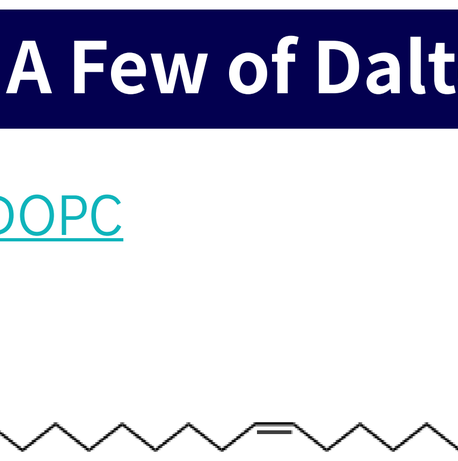
A Few of Dalton's GMP APIs

DOPC

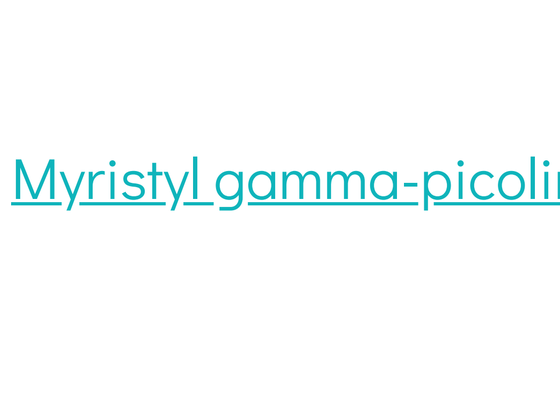
Myristyl gamma-picolinium chloride



L-Phenylalanine, 1-13C



Disodium boranocarbonate



For a full list of our GMP APIs, excipients and diagnostic reagents click here.

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