

Canadian Pharmaceutical GMP

Regulations Compared and Contrasted
to USFDA GMPs

by

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Reference Document Canada

- The Health Canada revised guidance Document entitled “Good Manufacturing Practices Guidelines” as provided for comment (December 8, 2006)
- http://www.hc-sc.gc.ca/dhp-mps/compliance/index_e.html
- Result of input from sub committees of the brand and Generic associations.

Reference Document

U.S.A

- 21 CFR Parts 210 and 211 – Current Good Manufacturing, Processing, Packing or Holding of Drugs; General and Current Good Manufacturing Practice For Finished Pharmaceuticals
- Revisions as of 2 May 2006

Canadian *Food and Drug Act*

- Has regulations attached to the Act.
- These Regulations are divided up into sections, these sections are called Divisions
- Division C.02 is that Division that pertains to Drugs.

Structure of the Canadian Guidance Document

- Introduction
- Purpose
- Scope
- Quality Management
- The Regulations
 - 29 regulations (C.02.002 to C.02.030)
 - Sorted under 16 sections.

Compare US FDA

- Part 210 General
- Status
- Applicability
- Definitions
- Part 211 CGMP for finished Pharmaceuticals
- 11 Subparts (A to K)

Part 211 cGMP for Finished Pharmaceuticals – 11 subparts

- A. General Provisions (2 sections)
- B. Organization and Personnel (4 sections)
- C. Buildings and Facilities (8 sections)
- D. Equipment (5 sections)
- E. Control of Components and drug Product Containers and Closures (7 sections)
- F. Production and Process Controls (8 sections)
- G. Packaging and Labeling Control (6 sections)
- H. Holding and Distribution (2 sections)
- I. Laboratory Controls (7 sections)
- J. Records and reports (9 sections)
- K. Returned and Salvaged Products (2 sections)

The Sections in the Canadian Guidance

- Regulation
- Sale
- Premises
- Equipment
- Personnel
- Sanitation
- Raw material Testing
- Manufacturing control
- Quality Control Dept.
- Records
- Packaging Material testing
- Finished Product testing
- Samples
- Stability
- Sterile Products
- Medical Gases

Layout of Canadian Guidance

- Section Title
- C.02.000
 - **REGULATION**
 - As worded in the Gazette
 - **RATIONALE**
 - Philosophical basis for the Regulation
 - **INTERPRETATION**
 - The details of what is expected to be in place to be compliance with cGMP

Guiding Principles USA compared to Canada

- US FDA “the regulations contain the GMP for methods to be used in and the facilities or controls to be used for the manufacture, processing, packaging, or holding of a drug to ensure that such drug meets the requirements of the act as to safety , and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.”
- Canadian “the holder of an establishment license must ensure that the fabrication, packaging, labelling, distribution, testing and wholesaling of drugs comply with these requirements and the marketing authorization and do not place consumers at risk due to inadequate safety and quality.”
- (Canadian directs the responsibility to a person.)

Canadian GMPs apply to

- Fabricators
 - Packager/Labeller
 - Importer (MRA and non MRA)
 - Distributor
 - Wholesaler
 - Tester.
-
- Different parts of GMP apply to each of these designated functions (Licensable Activities) within the pharmaceutical industry.

Example of Guidance Structure

- **PERSONNEL**

- **REGULATION**

- C.02.006

- Every lot or batch of a drug shall be fabricated, packaged/labeled, tested and stored under the supervision of personnel who, having regard to the duties and responsibilities involved have had such technical, academic and other training as the Director considers satisfactory in the interests of the health of the consumer or purchaser

- **RATIONALE**

- People are the most important element in any pharmaceutical operation, without the proper personnel with the right attitude and the right training it is almost impossible to fabricate, package/label, test or store good quality drugs.

- It is essential that qualified personnel be employed to supervise the fabrication of drugs. (continue next slide)

Example of Guidance structure (2)

- **PERSONNEL RATIONAL** (continued)
- The operations involved in the fabrication of drugs are highly technical in nature and require constant vigilance, attention to details and a high degree of competence on the part of employees. Inadequate training of personnel or the absence of an appreciation of production control often account for the failure of a product to meet the required standards.
- **INTERPRETATION**
 - Contains 26 items that express quantitative and qualitative expectations that constitute GMP. Like
 - 1.1 The individual in charge of the manufacturing department holds a Canadian University degree (or equivalent) in a science related to the work, has practical experience and directly controls and supervises.

Example of Guidance Structure (3)

- **PERSONNEL INTERPRETATION** Continued
 - 1.4 Qualifications of delegates are detailed
 - 7. Consultants and contractors have the necessary qualifications, training, and experience to advise on the subjects for which they are retained
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- **Useful Note**
- The guideline features redline/strikeout that clearly shows the evolution from the 2002 version

Major Changes 2002 to 2006

- Are in sections
- Personnel (C.02.006)
- Raw material testing (C.02.009)
- Quality Control Department (C.02.015)
- Finished Product Testing (C.02.019)
- Samples (C.02.026)
- Sterile Products (C.02.029)
- Glossary of Terms.

Glossary of Terms

A way to bring specificity to general wording of Regulations

- USA

- 22 Definitions

- Canada

- 104 Definitions
 - And
- 14 Acronyms

Examples of glossary specifics

- USA

- (15) *Quality control unit* means any person or organizational element designated by the firm to be responsible for the duties relating to quality control

- Canada

- **QUALITY CONTROL DEPARTMENT** a function maintained by a fabricator, that is responsible only to management , and that monitors the quality of production operations and exercises control over the quality of materials required for and resulting from those operations

Use of the Glossary (2)

- **SPECIFICATIONS** Means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:
 - (a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture , packaging, and use of the drug, including the identity, potency and purity of the drug, raw material or packaging material,
 - (b) a detailed description of the the methods used for testing and examining the drug, raw material, or packaging material, and
 - (c) a statement of tolerances for the properties and qualities of the drug , raw material, or packaging material.

Example from table of GMP allocations

GMP Regulations Applicable to Licensable Activities.

Section	regulation	Fabricator	Packager Labeller	Importer both MRA	Distributor	Wholesaler	Tester
1. Premises	C.02.004	√	√			√	
5 Raw material testing	C.02.009	√					√
9 Finished Product testing	C.02.018	√	√	√	√		√

Exemptions!

- Exemptions from requirements under C.02.012(2) and C.02.019(1) and (2) are provided for importers of drugs where all activities (fabrication, packaging/labelling and testing) are carried out in MRA countries)
- A; other regulatory requirements described in the *Food and Drug Regulations* apply.

MRA Importer Exemptions

- C.02.012(2) “Every fabricator and package/labeller...every distributor and importer of a drug shall maintain a system designed to ensure that any lot or batch of the drug fabricated and packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division”
- C.02.019(1) “Finished product testing shall be performed after receipt of each lot or batch of the drug on the premises in Canada of the packager/labeller, distributor; or

MRA Importer exemption

- C.02.019 (4) “If a drug is fabricated, packaged/labelled and tested in an MRA country at a recognised building the distributor or importer (into Canada) is not required to comply with the requirements for finished product testing if the
 - the address of the building is set out in that person’s establishment license and
 - That person retains a copy of the batch certificate for each lot or batch of the drug received by that person.

MRA Importer exemptions

- C.02.019 (cont) Shall perform finished product testing
- Subject to subsection (2) before receipt of each lot or batch of on the premises if
- A. the director has evidence that drug is manufactured to comply to GMP and meets the specification for the drug.

Mutual Recognition Agreements MRAs

- The agreements cover drug/medicinal products GMP compliance programmes.
- Equivalency of the programmes is determined according to a 3 phase confidence building process:
 - 1. Documentation review
 - 2. Evaluation of processes and procedures including an on-site evaluation; and
 - 3. Decision making on the results of the evaluation.

MRAAs and the European Community

- Became operational in February 2003 when all regulatory authorities (RAs) within the EU member states were thoroughly evaluated by the Health Products and Food Branch Inspectorate (HP FBI) and found to have equivalent GMP compliance programmes.
- And vice versa! The EC evaluated Canada's GMP compliance programme in 2000 and found us to be equivalent.

List of Countries with equivalent GMP compliance programmes.

- Austria
- Belgium
- Cyprus
- Czech Republic
- Denmark
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Malta
- Netherlands
- Portugal
- Spain
- Sweden
- United Kingdom (UK)

The benefits in plain language

- Canadian companies importing drugs/medicinal products that fall within the scope of the MRA and that are fully manufactured within an EC Members State in which the MRA is operational , may benefit from specified GMP exemptions provided by the MRA which are listed in the Canadian GMP guideline **AND**
- Canadian companies exporting drugs/medicinal products to any EC Member States that fall within the scope of the MRA and that are manufactured within Canada may benefit from specified GMP exemptions provided by the MRA.

Other EC countries in evaluation process

- Estonia
- Latvia
- Lithuania
- Poland
- Slovak Republic
- Slovenia
- Bulgaria
- Romania

Other countries for which MRAs exist

- Switzerland
 - Iceland
- Liechtenstein
 - Norway
- Australia.

Contrast to Sites in Non-MRA countries

- For testing other than identity testing (has to be done) and wish to rely on test results provided by an establishment in non MRA country then
 - Evidence of ongoing GMP compliance as demonstrated by listing on importer's establishment license and
 - 5 consecutive lots are tested and found to comply with the specifications.
 - Each lot has a certificate of analysis
 - Evidence that transportation/storage maintains the quality of the drug
 - Periodic testing (every 5 th batch or two per year)
 - A specific identity test is performed

Quality Management and the Canadian GMPs

- Not enough resources (Canada one tenth the population of US) and US not able to cope with all the foreign inspections.

Inspectorates stretched to the limit.

- GAO critical of FDA's overseas inspections
- By Nick Taylor, 23-Oct-2008
- Related topics: [QA/QC & validation](#)
- A report has been published detailing the US Food and Drug Administration's (FDA) failings in its inspection of overseas manufacturing facilities.
- The US Government Accountability Office (GAO) has released the report, which accuses the [FDA](#) of failing to keep accurate data about [overseas](#) drug facilities and not following up warning letters with inspections.
- In the fiscal years 2002 to 2007 the FDA issued 15 warning letters to overseas manufacturers citing serious deficiencies but failed to adequately follow these up, according to the report.
- The GAO found that after issuing the letters the FDA re-inspected four of the facilities but not until two to five years after it had initially discovered the faults.
- To remedy this situation the GAO has made five recommendations to the FDA, one of which suggests the agency should perform the same number of [inspections](#) overseas as it does in the US.
- Logistically this poses a considerable challenge, as at the current rate of overseas inspections it would take more than 13 years to visit all of them. In contrast, facilities in the US are inspected every 2.7 years on average.
- However, the exact time it would take to investigate the overseas facilities cannot be said with any great accuracy as the GAO found that the FDA does not now exactly how many sites ship drugs to the US.
- The FDA uses two databases to monitor [foreign](#) facilities. One lists establishments registered to market drugs in the US and the other is a database of facilities that have shipped drugs to the US, which contain around 3,000 and 6,800 sites respectively.
- In addition the GAO does not believe these numbers cannot be viewed as a definitive as it found that the FDA does not routinely verify that a registered establishment manufactures drugs for the US market.

Six-system Inspection Model

- The FDA's Inspection Drug Manufacturing Inspection Compliance Manual divided the functions in a pharmaceutical company into 6 (Six-system Inspection Model):
 1. Facilities & Equipment system
 2. Materials system
 3. Production system
 4. Packaging & Labeling system
 5. Laboratory Controls system
 6. Quality System

How to best use limited resources in Canada?

- Share the burden – MRAs
- Do not do Pre Approval Inspections
- Make companies responsible for complying with GMPs and to be self assessing as to their compliance
- Inspect self assessment program becomes focal point of GMP inspections.

Quality Systems

US approach

- FDA's Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations Sept 2006
- Describes a quality systems model which if implemented, will allow manufacturers to support and sustain robust , modern quality systems that are consistent with the CGMP regulations.
- Management Responsibilities “Management has ultimate responsibility to provide the leadership needed for the successful functioning of a quality system”
- Generate a Policy Manual embodies the Corporate commitment to the Quality System. The Company's “Hippocratic Oath”



Quality Systems

Canadian approach

- Embedded in the GMP guideline.
- Section 4 Quality Management
 - 4.1 GUIDING PRINCIPLE
 - 4.2 RELATIONSHIP AMONG QUALITY ELEMENTS
 - 4.2.1 QUALITY ASSURANCE
 - 4.2.2 GOOD MANUFACTURING PRACTICE (GMP) FOR DRUGS
 - 4.2.3 QUALITY CONTROL

Self assessment?

- **4.2.1 QUALITY ASSURANCE**
- 11. The effectiveness and applicability of the quality management system is ensured through regular self-inspection and management review.
- 12. An annual product quality review of all drugs should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both raw materials and finished product to highlight any trends and to identify product and process improvements.

A useful reference that lays out the role of the elements of Quality System Assessment .

- An article based on the four pillars of a Quality System by T Gerteisen
 - Document management.
 - Quality Assurance
 - Quality Control
 - Validation
- In the publication
 - PHARMACEUTICAL Canada
 - Vol 9 Num 2, Sept-Oct 2008
- A useful article to form the basis of a Quality Systems Manual

The Canadian Pharmacopeia?

- One exists – somewhere in the archives
- Instead Schedule B of the *Food and Drug Act* applies
- Schedule B contains four pharmacopeias
 - The USP
 - The BP
 - The EP and
 - The JP
 - If in doubt use the most stringent

Example reference to Schedule B

- **RAW MATERIAL TESTING C.02.009**
 - 3. Where a recognized pharmacopoeia (Schedule B of the *Food and Drug Act*) contains a specification for microbial content, that requirement is included
 - In US market destination has a similar effect on the microbial testing that will be required.

Manufacturing Control

C.02.011 & C.02.012

(cf F Production and Process Controls)

- Contains 114 specific directions required to be met to be in compliance with GMP.
- A section has been added “**ANNUAL PRODUCT QUALITY REVIEW**” and includes
- 51.2 A review of all batches that failed to meet established specifications and their investigation.
- 51.3 A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions

Annual Product Quality Review

- 51.4 A review of all changes carried out to the process or analytical methods
- 51.5 A review of the results of the continuing stability program and any adverse trends.
- 51.6 A review of all quality related returns, complaints and recalls and the investigations performed at the time.
- 51.7 A review of adequacy of any other previous process or equipment corrective actions.

Quality Control Department (cf I - Laboratory Controls)

- Detailed section on Microbiological media testing for performance.
- Includes a specific instructions on how to investigate Out of Specification (OOS) test results and a “may” instruction to refer to international guidelines on this topic. Which would include the FDA’s excellent guideline on OOS test results
- Detailed instructions on the nature of the technical agreement to ensure compliance of contractor testing.

Finished Product Testing (cf I - Laboratory Controls)

- Big difference is the MRA exemption
- RECOGNISED BUILDINGS BY A REGULATORY AUTHORITY IN A MRA COUNTRY
- 43. To demonstrate compliance with finished product specifications, importers of drugs fabricated, packaged/labelled and tested at recognized buildings authorized by a Regulatory Authority as listed in the regulations and identified on their establishment licence are required only to have a batch certificate in the format agreed on by the MRA partners for each lot or batch of the drug received. Retesting, including identity testing, is not required when the drug is fabricated, packaged/labelled, and tested in an MRA country

Records

(cf J - Records and Reports)

- Very similar.
- New addition to Canadian guideline,
- “1.3.2 Records are maintained detailing the qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides.”
- Causing a change to the role of consultants?

Samples

(cf 211.170 Reserve Samples)

- Note separation of responsibilities.
- 1. A sample of each lot or batch of a finished product is retained in Canada by the distributor and by the importer of the drug.
- 2. A sample of each lot or batch of a raw material (including both active and inactive ingredients) is retained by the fabricator of the drug
- (At least double the amount needed to complete all required tests.)

Stability (1)

(cf 211.166 Stability testing)

- C.02.027 “Every distributor and importer shall establish the period of time during which each drug in the package in which it is sold will comply with the specifications.” (same requirement (different wording) in both GMPs)
- C.02.028 “Every distributor and importer shall monitor by means of a continuing program the stability of the drug in the package in which it is sold” (not in US GMPs?)

Stability (2)

- The Canadian guideline includes a chart which is a guideline for selecting parameters (tests) to be studied in the stability program by product type. Each product must be examined separately. Product types are
- Tablets : Capsules : Liquids and Gels :
Ointments & Creams : Powders : Indictable :
Suppositories : Aerosols
- Of use in writing consistent stability protocols.

Sterile Products C.02.029

(cf occasional references in US GMPs)

- The Canadian **Regulation** (C.02.029) reads
- “In addition to the other requirements of this Division, a drug that is intended to be sterile shall be fabricated and packaged/labelled
 - (a) in separate and enclosed areas;
 - (b) under the supervision of personnel trained in microbiology; and
 - (c) by a method scientifically proven to ensure stability”

Sterile Products

- **The Rationale** reads
- “Sterile drugs are susceptible to particulate, pyrogenic and microbial contamination. Due to the health hazard associated with the use of contaminated sterile products, special precautions are required in the production of these products. The skill, training and competency of all personnel involved are critical. Quality assurance is important and the production must follow carefully established and validated methods of preparation and sterilization “

Sterile Products

- The approach taken by the Canadian guideline is to basically embed in this section a mini, but complete, GMP guideline specifically for Sterile Products. This section is very detailed and covers 22 pages of the full GMP guideline.

STERILE PRODUCTS

C.02.029

- This section contains the GMP requirements grouped under the following headings
 - General (although is highly specific)
 - Premises
 - Water Treatment Systems
 - Personnel
 - Sanitation
 - Manufacturing Control

Sterile Products

(C.02.029)

- Major additions to the current guideline are
 - Directions and standard w.r.t. filtered air supplies
 - Behavioral techniques of personnel in aseptic areas.
 - Filing operations
 - Sterilization by filtration.
 - Blow/fill/seal
 - Isolator technology and
 - Verification of vendor supplied media.

Medical Gases (C.02.030)

(Not covered in US GMPs)

- Canadian GMPs apply except for
 1. Do not need to keep samples.
 2. Do not need stability studies to support shelf life.
 3. Do not need to have a continuing stability program.

The Part of Tens (1)

- Offering food for extra thought.
- 1. Why are Canadian inspections more rigorous than US inspections?
- 2. How is Canada (and other countries) dealing with GMP issues in countries like India and China.?
- 3. PAT approach not yet built into the Canadian GMPs as such.
- 4. Supplies for Clinical studies in UK easier route via Canada than direct form USA.
- 5. Target cleaning levels for cytotoxic products are N.D. and self contained facilities are required.

The Parts of Ten (2)

- 6. Reference to ICH documents is made through out the guidelines e.g. ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology
- 7. All inclusive definitions (in SOPs) of deviations, non conformances or variations can lead to excessive numbers of investigation reports.
- 8. Quality Assurance is not a very good safety net
- 9. Don't sweat the semantic difference between Corrective and Preventative actions. Actions and their effectiveness is what counts!

Semantics?

- **Corrective**

- Action taken to eliminate the causes of an **existing** non-conformity, defect or other undesirable situation in order to prevent **recurrence**.

- **Preventative**

- Action taken to eliminate the cause of a **potential** non-conformity, defect, or other undesirable situation in order to prevent **occurrence** [ISO 8402]



The Parts of Ten (3)

- 10. A last thought,
- Who pays (\$) for a compliant Quality System, and is it becoming over burdensome?
- Scope based on Risk?
- Thank You

Preventive Action

- Action taken to eliminate the cause of a **potential** non-conformity, defect, or other undesirable situation in order to prevent occurrence [ISO 8402]