

Changes to HPFBI Good Manufacturing Practices (GMP) Guidelines

AUGUST 2009
A Comparison Between 2002
Version 2 and 2009 Editions



WHO DOES THIS APPLY TO:

- For pharmaceutical, radiopharmaceutical, biological, veterinary and disinfectant drugs:
 - Fabricators
 - Packagers/labellers
 - Distributors
 - Importers
 - Wholesalers
 - Testers

KEY POINTS:

- Good Manufacturing Practices (GMP) Guidelines, 2002 Edition Version 2, is still effective until November 8, 2009.
- Health Canada's Health Products and Food Branch Inspectorate (HPFBI) intends to implement further changes, mostly related to crimping of sterile vials, to be effective March 1, 2010.

SIGNIFICANT CHANGES IN THE 2009 EDITION:

- Changes to interpretations throughout to highlight HPFBI expectations.
- References to related guidance documents have been added.
- Individuals in charge of an importer or distributor quality control (QC) department must now have a Canadian university degree in a science related to the work being carried out.
- Annual Product Quality Reviews are now required.
- Alternate sample retention procedures have been removed and are now part of the Drug Establishment Licence renewal process.
- There are additional requirements for sterile product process simulation, changes to airborne particulate classification.

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Good Manufacturing Practices (GMP) Guideline 2009 Edition (GUI-0001) is available online at:

<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/index-eng.php>

Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069) is available at:

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069_tc-tm_e.html



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QUALITY MANAGEMENT:

- New requirement: Conduct an annual product quality review of all drugs.
- 'GMP Requirements for particular activities' table is now 'Chart 1.0: GMP Regulations Applicable to Licensable Activities'; importer MRA and non-MRA have been combined, and responsibilities have been added for all roles.

GLOSSARY OF TERMS:

- This has moved to Appendix B.

PREMISES C.02.004:

- Ensure external contamination of drug product residues in final container and primary packaging does not exceed acceptable levels for highly sensitizing drugs (e.g., penicillins, cephalosporins) and highly potent drugs (e.g., potent steroids, cytotoxics, vaccines).
- Self-contained facilities are required for highly sensitizing drugs and highly potent drugs in the absence of validated cleaning/inactivation procedures.

EQUIPMENT C.02.005:

- Computerized systems now included in equipment requiring installation and operational qualification.
- Equipment used for significant processing and testing operations is maintained in accordance with a written preventive maintenance program.

PERSONNEL C.02.006:

- Individuals in charge of quality control of a fabricator, packager/labeller, importer, distributor or tester, and individuals in charge of manufacturing for fabricator or packager/labeller require a Canadian university degree (or recognized equivalent) in a science related to the work being carried out.

SANITATION C.02.007 C.02.008:

- New requirement: Where necessary, sanitizers and disinfectants are filtered to remove spores (e.g., isopropyl alcohol).
- New reference to International Conference on Harmonisation (ICH) document for analytical method validation (ICH Q2).
- Clarification regarding hygiene requirements.
- No domestic washing of uniforms is allowed.

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RAW MATERIAL TESTING C.02.009 C.02.010:

- Purified water testing requirements have been expanded.
- Method transfer studies are conducted when applicable.
- Clarification on requirements for audit reports:
 - For medicinal ingredients/active pharmaceutical ingredients: Report should be issued by qualified authority demonstrating compliance. If an audit report is more than four years old or unavailable, a new audit is required by a qualified person.
 - For other raw materials: Audit report should be issued by a qualified person.
- Changes to testing requirements for raw materials:
 - In lieu of testing each container for identity, it is acceptable to test only a proportion of the containers where a validated procedure has been established.
 - Perform complete confirmatory testing on the first three lots of each raw material and after significant change to the manufacturing process (changed from first lot only). For modified processes, a new impurity and residual solvent profile is also obtained from the vendor.
 - Where a batch of raw material is handled in a substantial way (i.e., repackaged by a third party) after leaving the site of fabrication, sample each container and positively identify the contents.
- Change to periodic confirmatory testing requirements of raw materials to monitor vendor certification:
 - Complete testing is conducted on a minimum of one lot per year of any raw material received from each vendor, with the raw material being selected on a rotational basis.
 - New requirement: Where multiple raw materials are received from the same vendor, perform complete confirmatory testing for each raw material at least once every five years.

MANUFACTURING CONTROL C.02.011 C.02.012:

- Annual Product Quality Reviews are now required: Regular periodic or rolling quality review (i.e., annually) of all drugs to verify consistency of existing process and appropriateness of specifications to highlight any trends and to identify product and process improvements.
- Master formulae must specify requirements for maximum validated hold times for in-process material.

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- To ensure rapid recalls, wholesalers must obtain drug products from distributors/importers that hold an establishment license. A written agreement describing responsibilities is required.
- Wholesalers must obtain drug products from companies that hold an establishment licence, and a written agreement should clearly describe respective responsibilities where an importer or distributor assumes wholesaler's responsibilities related to recalls.
- Subcontractors of services must be authorized by the contract-giver (i.e., written authorization).

QUALITY CONTROL DEPARTMENT C.02.013 C.02.014 C.02.15:

- Clarification regarding finished product release:
 - Assessment should include review of storage and transportations conditions, if applicable.
 - Any non-conformances that may impact quality or product safety should be assessed and rationale documented pending release.
- Requirements for storage and transportation of drug products have been expanded (GUI-0069).
- New interpretations for laboratories:
 - Perform periodic environmental monitoring in microbiology labs and facilities used to perform sterility testing.
 - Lab computer systems are validated and spreadsheets are qualified.
 - Further guidance is available on how to investigate out-of-specification (OOS) test results to determine root cause, and how to ensure compliance of contractors conducting testing.
 - Contract laboratories must have a valid Canadian Drug Establishment Licence (DEL). Foreign labs must be listed on a Canadian DEL. Written authorization is required for any subcontracted work.

Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069) is available at:
http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069_tc-tm_e.html

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PACKAGING MATERIAL TESTING C.02.016 C.02.017:

- Two additional interpretations have been added on sampling plans:
 - For packaging materials, include quantity, nature of the material, production methods and supplier audits.
 - Ensure sampling takes place in a suitable environment.

FINISHED PRODUCT TESTING C.02.018 C.02.019:

- Clarification regarding product with OOS results: Quarantine pending final disposition, do not make available for sale.
- Requirements for finished product testing of product from non-MRA sites have been added:
 - Periodic complete confirmatory testing is performed on at least one lot per year per dosage form per fabricator. For each dosage form, products are selected on a rotational basis.
 - In addition, where multiple drugs are received from the same fabricator, confirmatory testing is carried out for each drug at least once every five years.
- Upon receipt of finished goods, ensure there is evidence that adequate environmental monitoring has been maintained for the storage and transportation of the drugs to support the quality of the drug.

RECORDS C.02.020-C.02.024:

- Keep records of qualification/experience and services provided for GMP consultants.

SAMPLES C.02.025 C.02.026:

- Clarification on expectation regarding sample containers.
- Retention samples may be stored at another site if it holds a Canadian Drug Establishment Licence and there is a written agreement outlining responsibilities of each party.
- Alternate sample retention procedures have been removed. (This is now part of the Drug Establishment Licence renewal process.)
- Health Canada will consider alternate sample retention sites outside of Canada for distributors and importers of drugs if an application is submitted.

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STABILITY C.02.027 C.02.028:

- Clarification on expectations regarding new chemical entities.
- Stability studies originating from foreign sites are acceptable for imported products, provided various Health Canada and ICH guidelines and GMP compliance requirements are met.
- Clarification on expectations regarding GMP compliance of studies from foreign sites.
- Requirements for stability studies are outlined in various Health Canada, International Conference on Harmonisation (ICH), and Veterinary ICH (VICH) guidelines.

STERILE PRODUCTS C.02.029:

- General:
 - Produce sterile products subject to neither filtration nor terminal sterilization in an aseptic area under a local Grade A zone with at least a Grade B background.
 - EU standards have been adopted for airborne particulate classification. (They are slightly less stringent.)
- Premises:
 - Additional guidance provided for air supply, including maintenance and monitoring requirements.
 - Ensure sterile fabricating environments meet the pressure differential specifications between grades as per the GMPs.
- Equipment:
 - Frequency of vent filter integrity testing defined with a requirement to investigate failures.
- Personnel:
 - Guidance is provided in regards to gowning requirements in various Grade environments.
 - Specific behavioural techniques are specified for aseptic areas.
- Sanitation:
 - Include sporicidal agents in the disinfectant program.
- Manufacturing Control:
 - Significant detail added for validation of aseptic processing with adoption of US standards for process simulation.

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- New sections have been added to address requirements for sterilization by filtration, blow/fill/seal equipment and isolator technology.
- Quality Control:
 - Review Grade A environmental data as part of batch release.

MEDICAL GASES C.02.030:

- No changes.

APPENDICES:

- Annex A – Table of designated regulatory authorities has been removed.
- Annex B – “Application for Alternate Sample Retention” has been removed. This activity is now part of the Drug Establishment Licence renewal process.
- Appendix B – Includes the list of Acronyms and Glossary of Terms, previously found at the beginning of the guidance document. Some new and modified terms are included in the Glossary of Terms.
- Appendix C (previously Annex C) – Updated to include the most recent website links. Adoption of numbering of Annexes to the main GMP Guidelines employed by Europe and the Pharmaceutical Inspection Cooperation Scheme (PIC/S). New guide numbers; titles are unchanged.

FAQs:

1. When will 2009 Edition booklets be available?

Quality & Compliance Services Inc. has a new bilingual GMP combination booklet available now.

2. What is an Annual Product Quality Review?

An Annual Product Quality Review is a comprehensive review of the chemistry, manufacturing, and quality metrics of a drug product. These are statistically reviewed to verify the consistency of the existing processes and specifications.

3. Why are there further revisions planned for March 2010?

Health Canada will be adopting EU standards for crimping once they are finalized. These standards are currently subject to comment.

4. What do I have to do differently regarding confirmatory testing?

- Raw Materials:
 - Complete confirmatory testing on the first three lots.

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- For multiple raw materials received from the same vendor, confirmatory testing is required for each raw material at least once every five years.
- For multiple drugs imported from the same fabricator in a non-MRA country, confirmatory finished product testing is required for each drug at least once every five years.

5. How do I meet the requirements for transportation and storage of drug products?

Read our Temperature Control QuickNote™ to learn what you need to do to meet the requirements of GUI-0069, *Guidance for Temperature Control of Drug Products during Storage and Transportation*.

Contact us to help you with your transportation and/or shipping validation activities. To view our QuickNotes™, go to our website, <http://www.qualityandcompliance.com>, and click QuickNotes in the navigation bar.

6. How can Q&C® help you?

As your full-service partner for compliance, we can meet all of your GMP needs. For more information, visit the Our Services section of our website, <http://www.qualityandcompliance.com>. We have solutions for your compliance challenges with:

- Quality Control Officer (QCO) Services: Our QCOs are fully qualified to assist or operate as your Quality Control department. They can advise you on how to meet the new testing requirements for raw materials, and they can complete or help with Annual Product Reviews.
- Validation Services: We offer full validation services. Our specialists can help you with validation of procedures, computer system IQ/OQ, development of a compliance program to meet the temperature control requirements of GUI-0069, and any other validation activities.
- Regulatory Services: We can guide you through the Drug Establishment Licence process, DIN applications, and various Common Technical Document modules.
- Laboratory Services: We can help you develop and maintain a cost-effective testing program to meet requirements for finished product testing where required.

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