OVERVIEW


It has been written with a view to harmonize with international GMP standards and terminology (e.g., ICH, PIC/S, WHO, etc.).

There is now an expectation that senior management participate actively in the pharmaceutical quality system, including periodic management reviews.

Plain language principles have been embedded. Explicit language has been added throughout to clarify current compliance expectations, such as data integrity, veterinary products, etc.

An enhanced confirmatory testing and auditing process has been established for products imported into Canada from non-MRA countries that do not have PIC/S oversight.

WHO DOES THIS APPLY TO?

For pharmaceutical, radiopharmaceutical, biological, veterinary and disinfectant drugs, and those preparing drugs to be used in clinical trials:

- Fabricators
- Importers
- Packagers
- Wholesalers
- Labellers
- Testers
- Distributors

KEY POINTS

Scope of GMPs increased to include drugs to be used in clinical trials

Premises, Equipment, Personnel, Sanitation

- No significant changes

Raw Material Testing

- Impurity specifications are now required for each active ingredient in a drug product formulation
Manufacturing Control

- Manufacturing control sections contain additional guidance for validation, and manufacturing master formula

Annual Product Quality Review

- All batches made using the same process, specifications, facilities, and formulation (not limited to batches received in Canada) must be included

- API fabricators must provide a copy of their APQR upon request (e.g., by Canadian establishment license holder)

Recall

- There is a formal expectation of mock recall evaluation to verify procedures, if no recalls have occurred

- Establishment license holders must provide Health Canada notification of any relevant and important information (e.g., FDA warning letter) communicated by a regulatory agency within 24 hours of the notification

- Additional guidance on Quality Agreements has been stated throughout. Explicitly stated:
  - Importer/Distributor assumption of wholesaler responsibility during recall must be outlined
  - Drug distribution supply chain arrangements must be outlined
  - Fabricators must confirm that API supplier buildings are compliant with Canadian GMP or ICH Q7 guidelines
  - The Contract Giver is ultimately responsible for the outsourced activities. They must assess records and results of the outsourced activities
  - The Contract Acceptor must be capable of carrying out the work in a competent and compliant fashion. Sub-contracting or changes to agreed activities require agreement from the Contract Giver
Quality Control Department

- Data Integrity expectations are stated specifically:
  - Data recorded at the time of generation, with reliable evidence to confirm this was done
  - Data organized, controlled and stored in a way that is interpretable and traceable (i.e., from the record source)
  - Systems, procedures, and practices in place to ensure records are reliable

- Increased detail is required for complaint investigations for product quality defects to evaluate the extent and determine the applicable root causes, based on the complaint risk

- Additional guidance has been given with respect to Out of Specification, Out of Trend, and atypical test results to ensure that record accuracy and reliability have been verified when conducting investigations

Packaging Material Testing

- No significant changes

Finished Product Testing

- Expectations are now stated:
  - Preservative testing must be completed when present in the drug product
  - All analytical test methods (compendia, non-compendia) must be validated

- No changes to MRA and confirmatory testing from PIC/S member countries (e.g., USA)

- Enhanced confirmatory testing requirements for non-MRA sites:
  - New requirement to conduct audits of foreign buildings and increased imported product retesting requirements

- Guidance on Parametric Release – PIC/S has been adopted by Health Canada
Records

- A data governance system must be established to ensure controls are in place to prevent and detect data integrity issues throughout the product lifecycle and for all records required under GMP

- Cloud computing is to be treated as a contracted service

- PIC/S Annex 11: Computerised Systems has been adopted by Health Canada for electronic records

Samples

- No significant changes

Stability

- The guidance document titled "Stability Testing of Existing Drug Substances and Products" previously referenced in GUI-0066 (Annex 1 to the Current Edition of the Good Manufacturing Practices Guidelines - Selected Category IV Monograph Drugs) has been replaced by “Evaluation of Stability Data: ICH Topic Q1E”

Sterile Products

- PIC/S guidance Annex 1 Manufacture of Sterile Medicinal Products has been adopted by Health Canada

- Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119) describes the interpretations to fulfill these expectations

General

- Veterinary guidance documents and requirements are now referenced explicitly throughout the guide

- GMP Annex 1 guidance for Category IV or OTC products has been separated from the GMPs and assigned GUI-0066. There are no changes to this document
WHAT DO I NEED TO DO?

1. Obtain the following documents, and conduct an audit to assess compliance:

   GUI-0001: Good Manufacturing Practices

   GUI-0023: Risk classification guide for drug good manufacturing practices observations

   ICH Q10: Pharmaceutical Quality System

   ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

2. Ensure Senior Management is aware of the increased expectation for their participation in the pharmaceutical quality system, including periodic management reviews, awareness of decisions that impact product quality or GMP compliance, evaluation of quality system effectiveness, and appropriate resourcing.

3. Ensure your quality system processes (e.g., Change Controls, Deviations) are used to drive continuous improvement that ensures product quality and site compliance.
4. If you are an Importer of products from a non-MRA country that is not inspected by a PIC/S member:

- Assess the country of origin for your products and assess MRA and PIC/S statements to determine required confirmatory test actions
- To maintain a reduced testing program, establish a vendor certification testing program to verify drug product testing results from non-MRA foreign sites that are not inspected by PIC/S members.

**Example:** Product received by a Canadian Importer from India (non-MRA, not PIC/S inspected), 20 unique batches per year

<table>
<thead>
<tr>
<th>Test requirement</th>
<th>Using a Vendor Certification program</th>
<th>No Vendor certification program in effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Test</td>
<td>Conduct full confirmatory testing of the first five (5) unique batches of any drug received from each foreign building*</td>
<td></td>
</tr>
<tr>
<td>Identity Test</td>
<td>Conduct identity testing on all 20 unique batches received</td>
<td>Fully confirmatory test all 20 unique batches of any drug each year</td>
</tr>
<tr>
<td>Periodic Confirmatory Test</td>
<td>Perform complete confirmatory testing on at least one (1) batches per year for each dosage form from each fabricator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Where multiple drugs are received from the same fabricator, carry out confirmatory testing for each drug at least once every five (5) years</td>
<td></td>
</tr>
</tbody>
</table>

*For facilities qualified prior to the implementation of this guide, ensure that testing of five (5) unique batches of any drug have been completed, and that at least one (1) batch of each drug has been tested.
## DEFINITIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>APQR</td>
<td>Annual Product Quality Review</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practices</td>
</tr>
<tr>
<td>HC</td>
<td>Health Canada</td>
</tr>
<tr>
<td>HPFBI</td>
<td>Health Product and Food Branch Inspectorate</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>ICH Q10</td>
<td>Pharmaceutical Quality System</td>
</tr>
<tr>
<td>ICH Q12</td>
<td>Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management</td>
</tr>
<tr>
<td>ICH Q7</td>
<td>Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines &amp; Healthcare Regulatory Agency (United Kingdom)</td>
</tr>
<tr>
<td>MRA</td>
<td>Mutual Recognition Agreement</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the Counter</td>
</tr>
<tr>
<td>PIC/S</td>
<td>Pharmaceutical Inspection Cooperation Scheme</td>
</tr>
<tr>
<td>Senior Management</td>
<td>Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site (ICH Q10 based in part on ISO 9000:2005)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
RELATED DOCUMENTS

Health Canada Guidance Documents

GUI-0001: Good Manufacturing Practices

GUI-0023: Risk classification guide for drug good manufacturing practices observations

ICH Guidance Documents

ICH Quality Guides

PIC/S Guidance Documents

PIC/S Publications

FAQ

1. **Will Q&C be updating the Blue Book?**

   Absolutely! Please contact us for further information, and to place pre-orders. [Online booklet ordering is available here.](#)

2. **Will Health Canada start enforcing this guidance now?**

   This document has an effective date of 01 October 2018; however, we’ve already observed Health Canada making observations against these requirements.

3. **What do the new vendor certification requirements mean for Canadian importers?**

   No changes have been made to either MRA or Non-MRA countries that are inspected by PIC/S members (including the USA). For other non-MRA countries, additional testing and auditing of non-PIC/S member countries are now required.
4. Who are the current PIC/S country members?

A listing of the current PIC/S members are included here. The current (01 January 2018) country list includes Argentina, Australia, Austria, Belgium, Canada, Chinese Taipei, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong SAR, Hungary, Iceland, Indonesia, Iran, Ireland, Israel, Italy, Japan, Republic of Korea, Latvia, Liechtenstein, Lithuania, Malaysia, Malta, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, United Kingdom, USA.

5. Have there been any updates related to data integrity expectations?

Yes. This update has formalized the requirements for data accuracy and reliability throughout the data lifecycle. Data governance and validation requirements have been clarified. We expect this to be an area of continued audit focus. In addition, the MHRA “Guidance on GxP data integrity” has also recently been finalized.

6. Has the scope of the GMP guidance changed?

Yes! Veterinary products and clinical trial materials have been included.

7. There has been a lot of added guidance regarding quality agreements. What do these updates mean?

Health Canada continues to emphasise the importance and requirements of quality agreements (especially during inspections); Quality Agreements should specify controls and responsibilities throughout the drug distribution supply chain.

Health Canada has established the expectation for Quality agreements to be established throughout the drug product supply chain (e.g., from Raw Materials, Fabrication, Packaging/Labelling, Testing, Importing, and Wholesaling, to Storage and Transportation).

New expectations include:

- An enhanced focus on making sure that any outsourcing or sub-contracting is adequately addressed in a way that ensures that product and site quality is maintained, and that each party is competent to do the work.
Formalized requirements for Importers to have quality agreements that include coverage for all foreign (Fabricate, Package, Label, Test) activity holders to ensure their effective oversight.

8. What other PIC/S changes are included in this update?

In addition to the above, Health Canada has adopted the following PIC/S guidance documents. These documents are used by PIC/S inspectors when collecting GMP evidence:

- Annex 1: Manufacture of Sterile Medicinal Products
- Annex 11: Computerised Systems

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