

**Administrative Arrangement under Article 15.3(g) of the Protocol
on the Mutual Recognition of the Compliance and Enforcement Programme
regarding Good Manufacturing Practices for Pharmaceutical Products**

Equivalence Maintenance Programme

This administrative arrangement is not intended to create rights or obligations under international or domestic law and, in line with Article 15(7) of the Protocol, is not subject of the provision of Chapter 29 of the CETA Agreement.

Between DG SANTE and Health Canada

Friday, November 16, 2018

DG Santé is a Directorate General of the European Commission.

Health Canada is a Federal department of the Government of Canada.

This administrative arrangement has been approved by the European medicines Agency (EMA) and the competent authorities of the Member States.

1. Introduction

The Equivalence Maintenance Programme is one of the main elements of the CETA GMP Protocol to the Mutual Recognition of the Compliance and Enforcement Programme regarding Good Manufacturing Practices for Pharmaceutical Products (CETA GMP Protocol) which the Parties, through the Joint Sectoral Group (JSG), are required to establish under Article 13 of the CETA GMP Protocol and through an Administrative Arrangement pursuant to Article 15.3(g) (Equivalence maintenance programme).

This Administrative Arrangement sets out the operational arrangements to fulfil the requirements of Article 13.

Article 13

Equivalence maintenance programme

1. *“The Joint Sectoral Group shall develop an equivalence maintenance programme under the GMP Administrative Arrangement referred to in Article 15.3 to maintain the equivalence of the regulatory authorities. The Parties shall act in accordance with this programme when deciding whether to change the equivalence status of a regulatory authority.*

2. *If the equivalence status of a regulatory authority changes, a Party may re-evaluate that regulatory authority. Any re-evaluation must be undertaken pursuant to the procedure set out in Article 12. The scope of re-evaluation shall be limited to the elements that caused the change of the equivalence status.*

3. *The Parties shall exchange all the necessary information to ensure that both Parties remain confident that equivalent regulatory authorities are in fact equivalent.*

4. *A Party shall inform the other Party before adopting changes to its technical guidance or regulations relating to good manufacturing practices.*

5. *A Party shall inform the other Party of any new technical guidance, inspection procedures or regulations relating to good manufacturing practices.”*

2. Purpose

In order to assure continued confidence in the status of equivalence between the Canadian and EU regulatory authorities (RA(s)), this Administrative Arrangement describes a system for regular confirmation of equivalence of the Participants' GMP Compliance Programme. The components of the GMP compliance programme and its implementation by the RAs is established in this Administrative Arrangement.

3. Scope

1. This equivalence maintenance programme (the programme) applies to:

- a. RAs listed in Annex 2 to the CETA GMP Protocol, which are determined to be equivalent pursuant to provisions of Articles 12.(3) and 12.(6) (Equivalence of new regulatory authorities of the CETA GMP Protocol).

- b. RAs that are legal successors of the authorities determined to be equivalent under paragraph a.
 - c. RAs which were recognized as equivalent under the EU-Canada Mutual Recognition Agreement (MRA) of 14 May 1998 and which, in light of Article 12.6 of the CETA GMP Protocol are recognized as equivalent at the time the CETA went into effect.
2. The programme includes the following:
- a. Evaluation of the changes to determine their impact on the delivery of the Participant's GMP compliance programme.
 - b. Monitoring of the RAs deemed equivalent under Articles 12.(3) and 12.(6) of the CETA GMP Protocol.
 - c. Integration of new RAs in the maintenance programme following the determination of equivalence under Articles 12.(3) and 12.(6) of the CETA GMP Protocol.
 - d. Making recommendations to the JSG for re-evaluation/deletion of RAs listed in Annex 2 to the CETA GMP Protocol.
 - e. Resolution and prevention of issues leading to loss of an RA's equivalency.
3. This programme aims to identify and evaluate significant changes in the Participant's legislation, or the RA's organizational structure, guidance documents, or inspection programme (scope, policies, and procedures) to ensure the continued equivalency of the GMP Compliance Programmes.
4. This programme ensures updates of contact persons for each RA notably for the Two-way Alert Programme and the exchange of certificates of GMP compliance.

4. Definitions

For the purposes of this Administrative Arrangement:

Compliance means abiding by the laws, regulations and standards;

Equivalency means leading to the same result but does not mean identical;

Significant changes means changes that may affect the equivalency, especially those related to the following critical sub-components of the GMP compliance programme established under Article 15.3(e) of the CETA GMP Protocol

- sub-component 1A – Empowering legislation
- sub-component 3A – Details/scope of GMP (including 3B – Process validation)
- sub-component 5E – Standard Operating Procedure for conducting inspections (including 5D – Inspection methodology)
- sub-component 7B – Non-compliance management (including 2B- Enforcement Policies, 7A-Provision of written notice of violations, 7D - Other measures)
- sub-component 8A – Alert mechanism (including 2E – Alert/crisis management, policies/procedures/guidelines, 8B – Crisis management mechanism)
- sub-component 9A – Access to laboratories
- sub-component 10C – Consumer complaint system
- sub-component 11A – Quality management system (including 2F – organisational structure, 6A – Performance standards)

Minor changes mean changes, which do not affect equivalency.

5. Individual Roles

- a. Each Participant manages the human resources of the RA and costs necessary for the RA to fulfil its duties.
- b. Each Participant reports on its activities under this Administrative Arrangement.

5.1 Joint Roles

- a. The Participants understand that the JSG will meet, make decisions regarding the management of the programme and communicate such decisions, and make recommendations to the CETA Committee on Trade in Goods, if necessary.
- b. Each Participant will inform the other Participant of any changes and activities that may adversely affect the equivalence of its GMP Compliance Programme, taking into account the elements defined on a basis of Article 15.3(e).

5.2 Roles of the Maintenance Representatives

The Participants understand that each Maintenance Representative (set out in paragraph 6 of this Administrative Arrangement) will provide:

- a. Information concerning changes to the contact persons of the RAs listed in Annex 2 of the CETA GMP Protocol;
- b. Documentation in the context of equivalency re-evaluation; and
- c. The annual report of the maintenance programme.

6. Maintenance Representatives

See Administrative Arrangement established under Article 15.3(c) *List of contact points in charge for matters arising under the CETA GMP Protocol*.

7. Elements and processes

The equivalence maintenance programme comprises four main elements:

- a. Inclusion in the maintenance programme;
- b. Maintenance and Re-confirmation of equivalence;
- c. Training; and,
- d. Exchange of information.

7.1. Inclusion in the maintenance programme

New RAs will be included in the maintenance programme following recognition of equivalence under Article 12 of the CETA GMP Protocol in accordance with the Administrative Arrangement under Article 15.3(f) *Procedure for evaluating new regulatory authorities*.

7.2. Maintenance and Re-confirmation

Participants will verify, at regular intervals, the continued fulfilment of the GMP Compliance Programme by their RAs. The Participants understand that the verification for maintenance and re-confirmation will consist of the following:

7.2.1 Maintenance

a. Annual Reports

- i. The Participants (RAs) will exchange an annual report to provide the status of their GMP Compliance Programme to the other Participants.
- ii. An example of the contents of an annual report is Appendix A of this Administrative Arrangement.
- iii. The Participants intend to evaluate the annual reports and take the reports into consideration when making decisions on the necessity for a desk-top evaluation and/or a triggered on-site re-assessment.

7.2.2 Desk-top evaluation

- a. The Participants understand that each RA should prepare a self-assessment every 5 years using a checklist in concordance with the Administrative Arrangement under Article 15.3(e) *Components of a GMP compliance programme*.
- b. Each Participant intends to evaluate the self-assessment of the RAs of the other Participant and specific information provided for in the desktop evaluation and, consider the outcome when deciding on the necessity for a triggered on-site re-assessment.
- c. If a Participant identifies significant changes within a RA of the other Participant, a report may be prepared in accordance with Appendix B, identifying the issue or deficiency. The report may be forwarded to the concerned RA and to the JSG.

7.2.3 Regular on-site re-assessments

- a. If no re-evaluation triggers are applied during the 9 years from the date this administrative arrangement was adopted by the JSG on Pharmaceuticals, the assessing Participant will determine the scope of the re-assessment based on the compliance history of the Regulatory authority and in consultation with the JSG.
- b. On-site assessments carried out by third parties within the past 9 years may be considered by the assessing Participant when deciding on the scope of the regular on-site re-assessment. In some circumstances, the assessed Participant may recommend a consultation with the JSG for the on-site re-assessment for reasons such as no new manufacturing sites or the existence of a recent equivalent evaluation or experience from joint inspections.

Re-confirmation

7.2.4. Triggered desktop evaluation

- a. Each Participant may carry out a desktop evaluation triggered by issues such as the outcome of the evaluation of the annual report of a RA, the sharing of information of changes in the GMP Compliance Programme of a RA or upon a specific request by the Participants. An approval of the JSG to such an evaluation may be needed in some circumstances.

- b. The Participants understand that the scope of such a specific evaluation will be in accordance with Article 13 of the CETA GMP Protocol and limited to the elements that may have caused the change of the equivalence status.

7.2.5. Triggered on-site re-assessments

- a. Each Participant may conduct an on-site re-assessment of the RA of the other Participant based on its own risk criteria and in particular in response to major reorganisation or failure in the maintenance of an equivalent GMP Compliance Programme with the prior approval of the JSG and the concerned RA.
- b. The Participants understand that the scope of the triggered on-site re-assessment will be in accordance with Article 13 of the CETA GMP Protocol and limited to the elements that have caused the change of the equivalence status.
- c. In order to save resources and minimise efforts, the Participants should, if possible, use synergies with other international assessments related to GMP Compliance Programmes.
- d. Each Participant may invite the other Participant to participate in an assessment programme (e.g. European Economic Area (EEA)-Joint Audit Programme (JAP), Pharmaceutical Inspection Co-operation Scheme (PIC/S)-Joint Reassessment Programme (JRP) or other internal assessments).

7.3. Training

- a. Each Participant should maintain a high level of qualifications of the GMP inspectors and other staff of the RAs set out in Annex 2 to the CETA GMP Protocol.
- b. Participants intend to promote the increase of the level of qualifications within the RA(s) through internal training, as well as training provided by other parties such as PIC/S and other MRA partners.
- c. The Participants understand that joint inspections they carry out will contribute to the on-going process of training, mutual learning and maintenance of equivalent inspection standards and approaches.

7.4. Exchange of information

- a. Participants envisage to actively exchange information as set out in Article 11 of the CETA GMP Protocol in a way clarified in the Administrative Arrangements established under Article 15.3 concerning matters such as: rapid alerts; GMP certificates; manufacturing/establishment licences; non-compliance information; suspected falsification/counterfeiting, product defects; and potential serious shortages or other intelligence pertaining to risks related to the quality/safety/efficacy of medicinal products, drugs, and active pharmaceutical ingredients (APIs).
- b. Participants may regularly, or upon request, exchange mutually the information on their inspection planning, minutes and relevant documents of GMP related meetings.
- c. If feasible, Participants may invite each other to observe or participate in GMP related meetings or training it organises, in order to contribute to harmonisation efforts and to maintain a common understanding and interpretation of GMP practices and requirements related to the supervision of the pharmaceutical industry as laid down in the GMP Compliance Programme.

7.5 Deviation from equivalence

If the evaluation of the significant changes indicates that the changes may affect the equivalence of the GMP Compliance Programme, the Participants will refer the matter to the JSG using the report template in Appendix B.

If the JSG concludes that the significant changes may effectively affect the equivalence status of a RA, the Participants will jointly decide on corrective measures with the concerned RA. The other Participant may then re-evaluate that RA in accordance with the procedure set out in Article 12 of the CETA GMP Protocol. The scope of the re-evaluation will be limited to the elements that caused the change of the equivalence status.

7.6 Regulatory Authorities deemed equivalent and subject to structural changes or reorganization

- a. Participants will inform each others of structural changes or any reorganization of the authorities involved in the GMP Compliance Programme.
- b. The Participants will provide each other's information in writing, preferably before implementation and in the annual report, explaining the impact of the changes on the GMP Compliance Programme.
- c. If a Participant's evaluation of the information received including any follow up clarifications indicates that the changes may affect the equivalence of the concerned regulatory authority, the Participants will refer the matter to the JSG.
- d. If the JSG concludes that the equivalence status of the RA has been adversely affected, the Participants will jointly decide on corrective measures with the concerned RA. The other Participant may then re-evaluate that RA in accordance with Article 12 of the CETA GMP Protocol. The scope of the re-evaluation will be limited to the elements that caused the change of the equivalence status.

7.7 Oversight

The Participants understand that the JSG will exercise oversight over the functioning of the equivalence maintenance programme.

7.8 Confidentiality

The Participants understand that article 14 of the CETA GMP Protocol (“Confidentiality”) applies to the sharing of information under this Administrative Arrangement.

8. Effective Date

This Administrative Arrangement will become operational on the date of its adoption by the Joint Sectoral Group on Pharmaceuticals.

9. Appendices

- A Template for the Annual Report of the Equivalence Maintenance Programme
- B Template for reporting of major issues arising from the GMP Compliance Programme

Appendix A

Example of contents of an **Annual Report of the Equivalence Maintenance Programme**

| | |
|---|--|
| Country | |
| Name of the Regulatory Authority | |
| Domain (human and/or veterinary) | |
| Coordinates of the Regulatory Authority (Address, phone number, fax number, website, etc.) | |
| Maintenance Representative - contact name and coordinates (Title, phone number, fax number, email, etc.) | |
| GMP Certificate contact name and coordinates (Title, phone number, fax number, email, etc.) | |
| Rapid-Alert System contact name and coordinates (Title, phone number, fax number, email, etc.) | |
| Reporting period | |
| Date of submission | |

- 1. Follow-up to outstanding issues from previous Annual Report(s) and/or last desk-top re-evaluation and/or on-site re-assessment**

- 2. Significant changes to the GMP compliance programme during the reporting period.**
 - 2.1 Legislative and regulatory requirements and scope
Sub-component 1A: Empowering legislation
 - 2.2 GMP Standards
Sub-component 3A: Details / scope of GMP (including 3B – Process validation)
 - 2.3 Inspection procedures
Sub-component 5E: SOP for conducting inspections (including 5D - Inspection methodology)
 - 2.4 Enforcement powers and procedures
Sub-component 7B: - Non-compliance management (including 7A - Provision for written notice of violations, 2B – Enforcement Policies and 7D – Other measures)
 - 2.5 Alert and crisis systems
Sub-component 8A: - Alert mechanisms (including 8B - Crisis management mechanisms and 2E – Alert/crisis management (policies/procedures/guidelines)
 - 2.6 Analytical capability
Sub-component 9A: Access to laboratories
 - 2.7 Surveillance Programme
Sub-component 10C-Consumer complaint system
 - 2.8 Quality management system
Sub-component 11A: Quality management system (including 2F – Organisational structure and 6A – Inspection performance standards)

3. **Changes to the GMP compliance programme, other than those related to critical sub-components (item 2 above), during the reporting period.**
4. **Internal /external assessments received during the reporting period**
5. **Training**
General information on training activities carried out
6. **Restructuring or reorganisation and impact on the Components of the GMP Compliance Programme (including planned reorganisation)**
7. **Exchange of information (incl. rapid alerts, inspection planning, GMP certificates and inspection reports)**
8. **Any comments or recommendations related to the maintenance programme**
Issues/recommendations regarding the Two-Way Alert programme, certificate of GMP compliance, etc.

Report prepared by:

Name

Title

Address

Phone number

Fax number

Email address

Appendix B

Template for reporting of major issues arising from the GMP Compliance Programme

1. Description of issue/deficiency, including the following additional information:
 - 1.1 date of identification of issue/deficiency
 - 1.2 source of information (e.g. issue/deficiency newly identified during monitoring programme or reported by third parties)
 - 1.3 identification of the RA where issue/deficiency was found
 - 1.4 identification of the RA concerned by the issue/deficiency (if also other RAs would be affected)
2. Identification of possible consequences of the issue/deficiency
3. Information about corrective measures proposed or taken by the R. A. and date
4. Conclusion and recommendation to the JSG and date
5. Supporting documentation