

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

Two - Way Alert 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 EU Member States.

1. Introduction

This Administrative Arrangement sets out the Two-Way Alert Programme which is one of the main elements of the *Protocol to the Canada – European Union Comprehensive Economic and Trade Agreement between the European Union and Canada on the Mutual Recognition of the Compliance and Enforcement Programme Regarding Good Manufacturing Practices for Pharmaceutical Products* (CETA GMP Protocol) that the Parties are required to establish for the purposes of complying with the requirements under Article 11.1 of the CETA GMP Protocol.

Article 11.1.

A Party shall, pursuant to the two-way alert programme under the GMP Administrative Arrangement referred to in Article 15.3:

- (a) ensure that a **restriction, suspension or withdrawal of a manufacturing authorisation** that could affect the protection of public health is communicated from the relevant regulatory authority in its territory to the relevant regulatory authority in the territory of the other Party; and*
- (b) if relevant, proactively notify the other Party in writing of a **confirmed report of a serious problem relating to a manufacturing facility** in its territory, or as identified through an on-site evaluation or inspection in the territory of the other Party, including a problem related to **quality defects, batch recalls, counterfeited or falsified medicinal products or drugs, or potential serious shortages**.*

2. Purpose

In order to protect Canadian and European Union (EU) consumers from potential health risks, the purpose of this Administrative Arrangement is to clarify the practical arrangements under which the Canadian and EU Regulatory Authorities (RAs), recognized in Annex 2 to the CETA GMP Protocol:

- notify the other Participant of confirmed defective product reports, corrective actions, recalls, falsification, fraud and potential or actual shortages due to manufacturing and quality problems related to products covered under the scope of Annex 1 to the CETA GMP Protocol;
- ensure that any suspension, restriction or revocation (total or partial) of a manufacturing authorisation in the case of the EU or an establishment licence in the case of Canada is communicated to the other Participant ;
- notify instances of serious non-compliance with the CETA GMP Protocol (requiring administrative action) by any manufacturer inspected by either Participant inside or outside its territory;
- respond to special requests for information relating to the above by the other Participant, and;
- maintain confidence in the functioning of the Two-Way alert programme under Article 11.1 of the CETA GMP Protocol.

3. Scope

The Two-Way Alert Programme applies to the human and veterinary medicinal products/ drugs covered in Annex 1 to the CETA GMP Protocol.

The Two-Way Alert Programme applies to the following situations that negatively affect or may negatively affect the quality of the products specified in Annex I to the CETA GMP Protocol:

- confirmed defective product reports, corrective actions, follow-up messages, or recalls;
- restriction, cancellation or suspension of a manufacturing authorisation or an establishment licence, in whole or in part, by a RA listed in Annex 2 to the CETA GMP Protocol;
- issuance of a GMP non-compliance statement and withdrawal or restriction of a GMP certificate by a RA listed in Annex 2 to the CETA GMP Protocol;
- counterfeiting, tampering, falsification, fraud;
- potential and actual shortages arising from any of these situations.

The Two-Way Alert Programme does not apply to pharmacovigilance or medical device alerts.

4. Confidentiality

Article 14 of the CETA GMP Protocol outlines the confidentiality obligations regarding the sharing of information.

The RA of one Participant will inform the RA of the other Participant within two working days of any effort made to obtain non-public information in cases when a judicial or legislative mandate orders disclosure of non-public information.

5. Mutual Notification

5.1 Procedure for the rapid exchange of information and data about life-threatening or serious medicinal product recalls (Rapid Alert Notification)

In order to provide a timely response to an identified real or potential hazardous situation, the speed and accuracy of communication to the RA of the other Participant is of utmost importance. The procedure for rapid exchange of information and data outlines ways and means to alert the other Participant RA with the appropriate degree of urgency.

5.1.1 In each case, a professional assessment i.e. a health risk assessment is made of the seriousness of the defect and its potential for causing harm to the consumer. Attachment 1 includes a definition of the classification of the urgency of defective medicinal products / drug alerts.

5.1.2 The health risk assessment, confirmed by the responsible RA, will determine the classification of urgency based on the degree of risk to the consumer. Alerts will be communicated to the other Participant based on the defined health hazard classifications of Class I and Class II in Attachment I.

5.1.3 The RA of the Participant will ensure that their respective designated contacts will communicate information and data based on verified and assured facts to the other Participant RA and in a timely manner. The minimum elements of the notification are described in Attachment 3.

5.1.4 The RA of the Participant will send Rapid Alert Notifications to the RA of other Participant for all **Class I** health hazards, irrespective of whether the product/batch was distributed to the jurisdiction of the other Participant or originated from the jurisdiction

of the other Participant or not. A Participant will notify the other Participant of all Class I alerts concurrent with the national notification.

- 5.1.5 The RA of Participants will send Rapid Alert Notifications to the other Participant RA for **Class II** defects. A Rapid Alert Notification will normally be sent to the other Participant except in cases where it is confirmed that the batch was not distributed in the jurisdiction of the RA other Participant. All Class II alerts should be notified concurrently with national notification.
- 5.1.6 **Class III** defects should not be notified through this Two-Way Alert Programme. However the RAs may exchange information about Class III recalls if it is of regulatory interest.
- 5.1.7 The detailed operational procedures applicable to issuing and handling of Rapid Alerts are set out:
 - for the EU, in the *Compilation of Union Procedures on Inspections and Exchange of Information*, and
 - for Canada, in *Recall Policy (POL-0016)*.

5.2 Procedure for the notification of confirmed defective product reports

- 5.2.1 In case of known distribution of a defective product in the jurisdiction of the RA of other Participant, the RAs of Participants may communicate envisaged measures arising from defective product reports such as; quarantine, recalls (Class I, II, III), GMP measures to avoid recurrence, distribution of a “caution in use” notice to healthcare professionals, relevant publication on the website, newsletter or similar.
- 5.2.2 The minimum contents of all Follow-up and Non-urgent information transmitted through the Rapid Alert System are detailed in Attachment 4. These notifications should have a reference number linking them to the original Rapid Alert notification.
- 5.2.3 The detailed operational procedures applicable to issuing and handling of defective product reports are set out:
 - a. for the EU, in the *Compilation of Union Procedures on Inspections and Exchange of Information*
 - b. for Canada, in *Recall Policy (POL-0016)*

5.3 Procedures for the notification of suspension or revocation of a manufacturing authorisation / establishment license, restriction/withdrawal of a GMP certificate and notification of non-compliance with GMP.

- 5.3.1 A RA of a Participant will notify the RA of other Participant of a suspension or revocation (total or partial) of a manufacturing authorisation/establishment license, and restriction/withdrawal of a GMP certificate.
- 5.3.2 The detailed operational procedures applicable to issuing notifications of suspension or revocation of a manufacturing authorisation/establishment license and restriction/withdrawal of a GMP certificate license are set out:
 - a. for the EU, in the *Compilation of Union Procedures on Inspections and Exchange of Information*, and
 - b. for Canada, in the
 - i. Policy 0001: Compliance and Enforcement Policy

- ii. Policy 0004: Drug Good Manufacturing Practices (GMP) and Establishment Licencing (EL) Enforcement Directive.
- 5.3.3 Notification of non-compliance with CETA GMP Protocol .
- 5.3.4 The detailed operational procedures applicable to issuing notifications of non-compliance with GMP are set out:
 - a. for the EU, in the *Compilation of Union Procedures on Inspections and Exchange of Information*, and
 - b. for Canada, in:
 - i. Policy 0001: Compliance and Enforcement Policy
 - ii. Policy 0004: Drug Good Manufacturing Practices (GMP) and Establishment Licencing (EL) Enforcement Directive.
- 5.4 Fraud and Counterfeit Products / Falsification:
 - 5.4.1 The RA of the Participants will use the Two-Way Alert System to notify each other of the possible presence in the distribution network of counterfeit/falsified products or those resulting from fraud in manufacture, packaging, labelling, distribution or promotion, and products containing counterfeit/falsified starting materials.
 - 5.4.2 The RA of the Participant in which the fraud or counterfeit or falsification activity was first detected will issue the notification containing the minimum contents detailed in Attachment 3.
 - 5.4.3 The detailed operational procedures applicable to fraud and counterfeit products or falsification are:
 - i. for the European Union, *The Compilation of Union Procedures on Inspections and Exchange of Information*
 - ii. for Canada *Policy on Counterfeit Health Products (POL-0048)*

6. Roles

6.1 General

- 6.1.1 RA(s) of each Participant should ensure that all actions put in place against manufacturers producing medicinal products (including APIs) that come within the scope of this Administrative Arrangement and which affect the protection of public health are communicated to the other Participant RA with the appropriate degree of urgency.
- 6.1.2 RA(s) of each Participant should ensure that the upkeep of and amendments to this document becomes an integral element of the system of maintenance from the effective date of the implementation of the Two-Way Alert Programme.

6.2 Product specific actions / recalls

- 6.2.1 The RA(s) of Participants should conduct recalls from the market of defective batches of medicinal products or drugs as set out in their respective legislation.
- 6.2.2 For a batch manufactured in or imported to an EU Member State, the RA of the Participant will issue the notification. Normally this is the Member State in which the defect was first identified.

6.2.3 For a batch manufactured in Canada, or a batch manufactured in a third country and imported into Canada, Health Canada will issue the notification.

6.2.4 In all cases, each Participant notifies the contacts set out in Attachment 2 pursuant to Article 11(3) of the GMP protocol.

6.3 All other notifications

The RA in each EU Member State and Canada will notify each other of any matter in accordance with sections 5.1, 5.2, 5.3 and 5.4 of this Administrative Arrangement as appropriate.

7. Language of Communication

RA(s) should notify the other Participant as required under this Administrative Arrangement in the English language.

8. Mode of Transmission

RA(s) will transmit information by e-mail or fax to the contact points, or through entry into the EudraGMDP database.

9. Effective date

This Administrative Arrangement is to come into operation on the date of the coming into force of the CETA.

Attachment 1

Rapid Alert System: Classification of Urgency of Defective Medicinal Product Alerts

CLASS I

Class I defects are potentially life threatening or could cause a serious risk to health and are notified through the Rapid Alert System in all cases.

Examples:

- Wrong product (label and contents are different products)
- Correct product but wrong strength, with serious medical consequences
- Microbial contamination of sterile injectable or ophthalmic product
- Chemical contamination with serious medical consequences
- Mix-up of some products (rogues) with more than one container involved
- Wrong active ingredient in a multi-component product, with serious medical consequences.

CLASS II

Class II defects could cause illness or mistreatment, but are not Class I. A rapid alert notification should be sent to all contacts on the rapid alert notification list as it might be difficult to know where a batch has been distributed. If the product distribution is known, the notification should be only sent to the contacts concerned.

Examples:

- Mislabelling, e.g. wrong or missing text or figures
- Missing or incorrect information (leaflets or inserts)
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- Chemical/physical contamination (significant impurities, cross-contamination, particulates)
- Mix up of products in containers (rogues)
- Non-compliance with specification (e.g. assay, stability, fill/weight)
- Insecure closure with serious medical consequences (e.g. cytotoxics, child-resistant containers, potent products).

CLASS III

Class III defects may not pose a significant hazard to health, but withdrawal of the products may have been initiated for other reasons. If deemed relevant by the issuing authority, the rapid alert system may be used.

Examples:

- Faulty packaging, e.g. wrong or missing batch number or expiry date

- Faulty closure
- Contamination, e.g. microbial spoilage, dirt or detritus, particulate matter

Attachment 2

Contact points pursuant to article 11(3) of the GMP Protocol

For Canada:

Manager, Health Product Compliance & Enforcement Unit

Regulatory Operations and Enforcement Branch (ROEB) Health Canada

14th floor, room 319, Jeanne Mance Building

200 Eglantine Driveway

Ottawa, Canada

K1A 0K9

Phone: (001) 613 954 0513

Fax: (001) 613 946 5636

Email : RapidAlert@hc-sc.gc.ca

For European Union:

The list of EU contact points for Rapid Alerts is updated and provided to Health Canada by the European Medicines Agency whenever it is updated.

Attachment 3

Minimum Contents of a Rapid Alert Notification of a Quality Defect or Recall

A Participant will endeavour to use internationally harmonised templates for the transmission of Rapid Alerts

The Participants should consider including in the rapid alert notification the elements listed below, as appropriate:

1. Reference Number
2. Addressee (To:)
3. Product Recall Class of Defect: I or II (to be specified)
4. Falsification / Fraud (to be specified)
5. Product(s) affected
6. Marketing Authorisation Number and Use in humans or animals (to be specified)
7. Brand/Trade Name
8. INN or Generic Name
9. Dosage Form
10. Strength
11. Batch/Lot Number (and bulk, if different)
12. Expiry Date
13. Pack size and Presentation
14. Date Manufactured
15. Marketing Authorisation Holder (in the reporting Participant)
16. Manufacturer (name and address), Contact Person and Telephone
17. Site where the defect occurred (in case the defect is attributed to a manufacturing site)
18. Recalling firm (if different from manufacturer), Contact Person and Telephone
19. Recall Number Assigned
20. Details of Defect/Reason for Recall
21. Information on distribution including exports (type of customer, e.g. hospitals)
22. Action taken by Issuing Authority and/or Proposed Action
23. Issuing Authority name (From:)
24. Contact Person at the issuing authority and telephone
25. Signature
26. Date
27. Time

Attachment 4

Minimum Contents of Follow-up and Non-urgent Information for Quality Defects

Each Participant will endeavour to use internationally harmonised templates for the transmission of Follow-up and Non-urgent information

The Participants should consider including the elements listed below, as appropriate in the notification:

1. Addressee (To:)
2. Recall Number Assigned and national reference number (if applicable):
3. Product
4. Marketing Authorisation Number
5. Brand/Trade name
6. INN or Generic Name
7. Dosage form
8. Strength
9. Batch number (and bulk, if different)
10. Marketing Authorisation holder
11. Manufacturer and contact person
12. Subject title and description of the issue
13. Issuing Authority (From:)
14. Issuing Authority Contact Person
15. Signature
16. Date
17. Time