



**PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME**

PI 010-5
3 Appendices
1 July 2017

STANDARD OPERATING PROCEDURE

PROCEDURE FOR HANDLING RAPID ALERTS AND RECALLS ARISING FROM QUALITY DEFECTS

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1. DOCUMENT HISTORY

Adoption by the PIC/S Committee	24 April 2002
Entry into force	1 July 2002

2. INTRODUCTION

- 2.1 In order to protect public health and animal health it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product during its marketing period or an investigational product during clinical trials.
- 2.2. Each holder of an authorisation is required to implement an effective procedure for the recall of defective products. The authorisation holder is required to notify the relevant Competent Authority of any defect that could result in a recall and indicate, as far as possible, the countries of destination of the defective product.
- 2.3 Each Competent Authority should have a written procedure for the issue, receipt and handling of notifications of defective products, batch recalls and other rapid alerts during and outside normal working hours.
- 2.4 The Competent Authority should assist the authorisation holder in the recall process, as appropriate, and monitor its effectiveness. The Competent Authority should ensure that information concerning the recall of medicinal products is notified rapidly to other parties, if the nature of the defect presents a serious risk to public health. This information should be transmitted by means of the “Rapid Alert System” described in this document.
- 2.5 In the present document a Competent Authority means a National Medicines Regulatory Authority, which is covered by a bilateral or a multilateral agreement such as the PIC/S Scheme, the EU Treaties, a MRA or a MoU.

- 2.6 This SOP is in line with the EU document “Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects”, as contained in the Compilation of European Union Procedures on Inspections and Exchange of Information, published by the EMA. If the EU document is amended, then the present document should be adapted accordingly.

3. PURPOSE AND SCOPE

- 3.1 This procedure covers transmission of information by means of a Rapid Alert between the different parties relating to the recall of medicinal products which have quality defects or which are falsified when urgent action is required to protect public health and animal health.
- 3.2 The procedure may be used also for transmission of other information such as cautions-in-use, product withdrawals for safety reasons or for follow-up messages to any of the above listed categories.
- 3.3 This procedure covers both human and veterinary medicinal products and operates within the scopes of the relevant Rapid Alert programmes established between the involved parties.
- 3.4 The procedure may also be used to notify quality defects, falsification or fraud in active pharmaceutical ingredients or investigational medicinal products when deemed relevant by the issuing authority.
- 3.5 Pharmacovigilance and Medical Device alerts are not included within the scope of this procedure.

4. CRITERIA FOR ISSUING A RAPID ALERT

- 4.1 The aim of the Rapid Alert System is to transmit only those alerts whose urgency and seriousness cannot permit any delay in transmission. To ensure its effectiveness, the system must not be saturated by the transmission of less urgent information. In each case a professional assessment must be made of the seriousness of the defect, its potential for causing harm to the patient or (in the case of a veterinary product) harm to animals, consumers, operators and the environment, and the likely distribution of the affected batch(es). Appendix 1 provides guidance on the classification of the urgency of the recall of defective medicinal products.
- 4.2 **Class I** defects are potentially life threatening. A Rapid Alert notification must be sent to all contacts of the rapid alert notification list, irrespective of whether or not the batch was exported to that country.
- 4.3 **Class II** defects could cause illness or mistreatment, but are not Class I. A Rapid Alert notification should be sent to all contacts of 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.
- 4.4 **Class III** defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons. These are not normally notified through the Rapid Alert System.

- 4.5 Where appropriate, the Rapid Alert System may be used for notification to authorities concerned of the recall of products or an embargo on the distribution of products following suspension or withdrawal of a manufacturing / wholesale authorisation.

5. ISSUE OF A RAPID ALERT NOTIFICATION

Responsibility

- 5.1 The Competent Authority in which the defect was first identified should investigate the defect and issue the Rapid Alert.
- 5.2 In the case of a parallel import, the Competent Authority in which the defect was first identified should issue the rapid alert.

Format of the Rapid Alert and its transmission

- 5.3 A suitable format for the notification of quality defects by the Rapid Alert System is given in Appendix 2. The form should be completed clearly in English. The notification and relevant documents should be sent to the rapid alert contact list by electronic mail. The contact list and any relevant documents should be attached to the notification.

The electronic mail message should use a unique subject line to identify the rapid alert and any follow-up messages. The subject line should consist of the following:

RapidAlert; [QDefect / Falsification / Fraud], Class [I / II]; Product [Name / INN], Action [Recall / No Recall / Follow-up], Rapid alert reference number. (For example RapidAlert; QDefect; I, ProductX; Follow-up,CH/I/07/01).

The rapid alert should be given a unique reference number with the following format:

Country code (country where the original alert was issued)/Region or Authority code (where applicable)/classification/sequential number/correspondence number. (For example ES/II/05/02 would indicate a class II rapid alert initiated by Spain, being the 5th rapid alert initiated by Spain and that it is the second correspondence regarding this rapid alert.)

- 5.4 Transmission of a Class I Rapid Alert must be concurrent with the national action. Whenever feasible, transmission of a Class II Rapid Alert should be concurrent with the national action, but in all cases should be within 24 hours of the national notification.

In the case of a Class I notification, it may be necessary to alert authorities in different time zones in addition by telephone.

When an authority issues a further rapid alert for a batch, the field 18 in the form in Appendix 2 "Detail of Defect/Reason for recall" should begin with the text: "Rapid Alert following original rapid alert #ref. no. #"

Rapid alert contact list

- 5.5 In line with the co-operation agreement between PIC/S and the European Medicines Agency (EMA), the latter maintains the contact list for the rapid alert notifications including all PIC/S members. Members of the list are human and veterinary authorities of EEA including acceding countries, MRA, PIC/S and international organisations (European Commission, EDQM, WHO). There is normally one contact per Competent Authority, which is officially nominated. Changes to contact names or details must be notified to the EMA (qdefect@ema.europa.eu) and are circulated immediately to the entire list by electronic mail. Contact details include telephone and fax numbers, electronic mail address, which should be monitored at all times. The PIC/S Secretariat is responsible for updating the EMA on contact details of non-EEA, non-MRA PIC/S Participating Authorities, once they apply to the Scheme.

6. FRAUD AND FALSIFIED PRODUCTS

- 6.1 The Rapid Alert System should be used to notify parties of the possible presence in the legal distribution network of falsified products or those resulting from fraud in manufacture, packaging, distribution or promotion and products containing falsified starting materials.
- 6.2 The Competent Authority which has first detected the fraud or falsification, should issue the notification. The format for the Rapid Alert notification in Appendix 2 may be used, but the heading on the document should make clear that the notification relates to fraud or to a falsified product and sufficient information should be provided under “details of defect” to enable it to be identified. Notification should be sent to the entire contact list.

7. FOLLOW-UP ACTION

- 7.1 Each Competent Authority should have written procedure to describe follow-up action to Rapid Alert notification.
- 7.2 The Competent Authority to which a recalled product was exported should monitor the conduct and effectiveness of any national recall that it initiates as a result of the Rapid Alert notification.
- 7.3 The relevant Competent Authority should investigate the circumstances which led to the distribution of the defective product and ensure that any necessary corrective action is taken by the manufacturer and marketing authorisation holder as appropriate.
- 7.4 All follow-up actions transmitted through the Rapid Alert System should use the form for follow-up and non-urgent messages for Quality Defects detailed in Appendix 3 to separate it from Rapid Alerts. It should have a reference number linking it to the original Rapid Alert following the same format as described above.

8. FURTHER USE OF RAPID ALERT CONTACT LIST

Although the contact list for rapid alert notifications shall be only used for the transmission of notification falling in the scope of this procedure and the GMP non-compliance procedure, in exceptional cases, if deemed relevant by the Competent Authority, the list may be used for the communication of other important and urgent information related to pharmaceutical products. These messages should clearly identify the subject and whether they are for information or action.

9. APPENDICES

- 9.1 Appendix 1: Classification of Rapid Alerts
- 9.2 Appendix 2: Format for Rapid Alert notification of a quality defect
- 9.3 Appendix 3: Format for Follow-up and non-urgent information for Quality Defects

10. REVISION HISTORY

Date	Version Number	Reasons for revision
1 July 2004	PI 010-2	Change in the Editor's co-ordinates
25 September 2007	PI 010-3	Change in the Editor's co-ordinates
1 January 2011	PI 010-4	Extend scope to APIs and investigational medicinal products; Change transmission of notifications from fax to email; Circulate Class I and Class II defects; Replace the terms "counterfeit" and "counterfeited" by "falsification" and "falsified", respectively
1 July 2017	PI 010-5	Change in RA notification (new point 15.2 on site where defect occurred)

**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. These must be 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 of 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 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

RAPID ALERT NOTIFICATION OF A QUALITY DEFECT / RECALL
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IMPORTANT -- DELIVER IMMEDIATELY

		Reference Number
[add letter head of sender]		
1. To: (see list attached, if more than one)		
2. Product Recall Class of Defect: I II (circle one)	I	3. Falsification / Fraud (specify)*
4. Product:	5. Marketing Authorisation Number: * For use in humans/animals (delete as required)	
6. Brand/Trade Name:	7. INN or Generic Name:	
8. Dosage Form:	9. Strength:	
10. Batch number (and bulk, if different):	11. Expiry Date:	
12. Pack size and Presentation:	13. Date Manufactured: *	
14. Marketing Authorisation Holder*:		
15. 1 Manufacturer: Contact Person: Telephone:	16. Recalling Firm (if different): Contact Person: Telephone:	
15.2 Where the defect is attributed to a manufacturing site, site where defect occurred (if different from 15.1): Contact Person: Telephone:		
17. Recall Number Assigned (if available)±		
18. Details of Defect/Reason for Recall:		
19. Information on distribution including exports (type of customer, e.g. hospitals): *		
20. Action taken by Issuing Authority:		
21. Proposed Action:		

22. From (Issuing Authority):		23. Contact Person:
		Telephone:
24. Signed:	25. Date:	26. Time: *

* Information not required, when notified from outside EU.

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APPENDIX 3

**FOLLOW-UP AND NON-URGENT INFORMATION
FOR QUALITY DEFECTS**

[add letter head of sender]		
1 To: (see list attached, if more than one)		
2 Recall Number Assigned:	2a National reference number (When applicable)	
4 Product:	5 Marketing Authorisation number:	
6 Brand/Trade name:	7 INN or Generic Name:	
8 Dosage form:	9 Strength:	
10 Batch number (and bulk, if different):		
14 Marketing Authorisation holder:		
15 Manufacturer:	16 Contact Person:	
17 Subject title <i>Add bulk message here</i>		
22 From (issuing Authority):	23 Contact person:	
24 Signed:	25 Date:	26 Time: