EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

European Medicines Agency
Inspections

London, 18 May 2009
EMEA/INS/GMP/313510/2006 Rev 1

COMPILATION OF COMMUNITY PROCEDURES ON INSPECTIONS AND EXCHANGE OF INFORMATION

PUBLISHED IN AGREEMENT WITH THE EUROPEAN COMMISSION BY EMEA (EUROPEAN MEDICINES AGENCY)

PROCEDURE FOR HANDLING RAPID ALERTS ARISING FROM QUALITY DEFECTS

[pending adoption]

This document forms part of the Compilation of Community Procedures on Inspections and Exchange of Information. Please check for updates on the EMEA website.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: gmp@europa.emea.eu http://www.emea.europa.eu

PROCEDURE FOR HANDLING RAPID ALERTS ARISING FROM QUALITY DEFECTS

Title:	Procedure for Handling Rapid Alerts Arising from Quality Defects
Date of adoption:	[pending adoption]
Date of entry into force:	1 September 2009
Supersedes:	Version in force 20 September 2006.
Reason for Revision:	Transmission of notifications changed from fax to email, Class I and II defects to be circulated to all contacts on notification list. The scope was extended to include APIs and IMPs.
Notes:	Pharmacovigilance or medical device alerts are not included within the scope of this procedure.

Contents:

Procedure for Handling Rapid Alerts Arising from Quality Defects

1. Scope

This procedure covers the transmission of information by means of a rapid alert between Competent Authorities in the European Economic Area (EEA) (the "Member States"), EU accession countries, PIC/S participating authorities, MRA partner authorities and international organisations (Council of Europe/EDQM, WHO, European Commission) relating to the recall of medicinal products which have quality defects, including counterfeit or tampered products, when urgent action is required to protect public health and animal health. 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. This procedure covers both human and veterinary medicinal products and operates within the scope of the relevant Two Way Alert programmes established between the Community and MRA partners.

The procedure may also be used to notify quality defects, counterfeit or fraud in active pharmaceutical ingredients or investigational medicinal products when deemed relevant by the issuing authority.

Pharmacovigilance or Medical Device alerts are not included within the scope of this procedure.

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 referred to in Article 40 of Directive 2001/83/EC or Article 44 of Directive 2001/82/EC (for veterinary products) is required by Article 13 of Directive 2003/94/EC or Article 13 of Directive 91/412/EEC (for veterinary products) 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. In addition, for centrally authorised products Council Regulation EC/726/2004, Art. 16(2) or Article 41(4) (for veterinary products) the marketing authorisation holder is obliged to keep the EMEA informed of certain new information (e.g. restrictions of supply).

2.4. 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.

2.5. The Competent Authority of each Member State 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 Member States, 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".

3. Criteria for Issuing a Rapid Alert

3.1. 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.

3.2. 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.

3.3. 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.

3.4. 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.

3.5. Where appropriate, the rapid alert system may be used for notification to Member States or MRA partners of the recall of products or an embargo on the distribution of products following suspension or withdrawal of a manufacturing / wholesale authorisation.

4. Issue of a Rapid Alert Notification

Responsibility

4.1. For a batch manufactured in a Member State, or a batch manufactured in a third country and imported into the EEA, which is the subject of a national or mutually recognised (decentralised) marketing authorisation, the Competent Authority of the Member State in which the defect was first identified should investigate the defect and issue the rapid alert.

4.2. In the case of a centrally authorised product, and in the exceptional case of a product that has both a centralised and a national authorisation, the Competent Authority of the Member State in which the defect was first identified should lead the investigation of the defect and issue the rapid alert (the issuing authority). The alert should include a recommendation on proposed action for all affected authorities.

When time allows, the content of the proposed action should be agreed with the supervisory authority, the EMEA and the CxMP rapporteur. In some circumstances and especially when the Supervisory Authority has conducted all the investigations, the Member State in which the defect was first identified may delegate to the Supervisory Authority the issuing of the Rapid Alert.

When, due to the urgency of the defect there is not sufficient time to develop a harmonised proposed action this section of the Rapid alert notification should inform all recipients that EMEA will co-ordinate further action in co-operation with the relevant Supervisory Authority, in accordance with EMEA's Crisis Management Procedures and that harmonised follow-up actions will be transmitted when ready.

4.3. In the case of parallel distribution of a centrally authorised product and where no repackaging is carried out, the procedure described under 4.2 applies. This procedure also applies if the defect resulted from a repackaging operation. Where repackaging is carried out but the defect results from the original manufacturing process, the procedure described under 4.2 still applies, but the rapid alert should include descriptions of the different packaging in which the product might appear (for example different language versions and pack sizes) where this information is available from EMEA.

4.4. In the case of a parallel import, the Competent Authority of the Member State in which the defect was first identified should issue the rapid alert.

Format of the rapid alert and its transmission

4.5. 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 send 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 / Counterfeit / 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.)

4.6. 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

4.7. EMEA maintains the contact list for the rapid alert notifications. 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 authority nominated by each member state. Changes to contact names or details must be notified to EMEA (qdefect@emea.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.

5. Fraud and Counterfeit Products

The Rapid Alert System should be used to notify competent authorities of the possible presence in the legal distribution network of counterfeit products or those resulting from fraud in manufacture, packaging, distribution or promotion and products containing counterfeit starting materials.

The Competent Authority of the Member State or MRA partner in which the fraud or counterfeit was first detected 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 counterfeit 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.

6. Follow-Up Action

Each Competent Authority should have a written procedure to describe follow-up action to a rapid alert notification. The Competent Authority of each Member State and MRA partner 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.

The relevant Supervisory Authority should investigate the circumstances that 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.

EMEA should co-ordinate follow-up action for recalls of centrally authorised products.

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.

7. 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. For example, EMEA disseminates urgent information from its scientific committees in this way.

8. Appendices

8.1. Appendix 1: Classification of Rapid Alerts
8.2. Appendix 2: Format for Rapid Alert Notification of a Quality Defect
8.3. Appendix 3: Format for Follow-up and non-urgent information for Quality Defects.

Appendix 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. 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

Appendix 2

IMPORTANT - DELIVER IMMEDIATELY

Rapid Alert Notification of a Quality Defect / Recall

	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)		3. Counterfeit / 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. Manufacturer†: Contact Person: Telephone:	16. Recalling Firm (if different): 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.

† The holder of an authorisation referred to under Article 40 of Directive 2001/83/EC or Article 44 of Directive 2001/82/EC and the holder of the authorisation on behalf of whom the Qualified Person has certified the batch for release in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC if different.

****

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[1]:	16	Contact Person:	
17	Subject title *Add bulk message here*			
22	From (issuing Authority):	23	Contact person:	
24	Signed:	25	Date:	26 Time:

[1] The holder of an authorisation to under Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC and the holder of the authorisation on behalf of whom the Qualified Person has certified the batch for release in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC, if different