

## **DECISION**

**No. 8/09.03.2007**

### **on the approval of procedure for handling Rapid Alerts and recalls arising from quality defects**

The Scientific Council of the National Medicines Agency, set up based on Minister of Public Health Order no. 485/09.05.2005, as amended through Minister of Public Health Order no. 159/22.02.2006, no. 1599/12.12.2006 and no. 395/27.02.2007, reunited on summons of the National Medicines Agency President in the ordinary meeting of 09.03.2007, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as further amended, agrees on the following

## **DECISION**

**Single article.** – The procedure for handling rapid alerts and recalls arising from quality defects is approved, according to the Annexes which are integral part of this decision.

**PRESIDENT  
of the Scientific Council  
of the National Medicines Agency**

**Acad. Prof. Dr. Victor Voicu**

**PROCEDURE**  
**for handling Rapid Alerts and recalls arising from quality defects**

CHAPTER I

**Scope**

Art. 1. – (1) This procedure is a translation into Romanian and an adaptation of Procedure EMEA/INS/GMP/313510/2006 for handling Rapid Alerts and recalls arising from quality defects, issued by the European Medicines Agency.

(2) This procedure has been issued in compliance with provisions of Art. 832 (2) of Law No. 95/2006 on healthcare reform, Title XVII-The medicinal product which transposes the updated Directive 2001/83/EC.

Art. 2. – (1) This procedure covers the transmission of information by means of a rapid alert between the Competent Authorities of the European Union (EU) and the European Economic Area (EEA) (“Member States”), Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries (CADREAC), Pharmaceutical Inspection Cooperation Scheme (PIC/S), European Directorate for Quality of Medicines and Healthcare (EDQM) and Mutual Recognition Agreement (MRA) partners, 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.

(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) Pharmacovigilance Alerts are not included within the scope of this procedure.

CHAPTER II

**Introduction**

Art. 3. - 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 batches of a medicinal product during its marketing period.

Art. 4. – (1) Each holder of a Marketing Authorisation, in Art. 748 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, is required, in compliance with provisions of Art. 38 of the Minister of Public Health Order No. 905/2006 on the approval of Principles and Guidelines of Good Manufacturing Practice for medicinal products for human use, including investigational medicinal products, to implement an efficient withdrawal procedure of defective products.

(2) The Marketing Authorisation Holder should inform the National Medicines Agency (NMA), concerning any non-compliance which could lead to a withdrawal and indicate, as much as possible, the countries in which the defective product has been exported.

Art. 5. - Moreover, for centrally authorised products, in compliance with Art. 15 (2) of the Council Regulation 2309/93, the Marketing Authorisation Holder is obliged to keep the European Medicines Agency informed of certain new information (e.g. suspension of the manufacturing authorisation, FDA Warning Letters, etc).

Art. 6. – The NMA should have a written procedure that covers the receipt and handling of notifications of suspected defective products and batch recalls from companies or health professionals both during and outside normal working hours.

Art. 7. – The NMA should assist the authorisation holder in the recall process, as appropriate, and monitor its effectiveness. The NMA 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”.

Art. 8. – The NMA should have a written procedure that covers the issue of rapid alerts both during and outside normal working hours (if the urgency of the situation warrants such action).

### CHAPTER III

#### **Criteria for issuing a rapid alert**

Art. 9. – (1) The aim of the Rapid Alert System is to transmit only those alerts whose urgency and seriousness cannot permit any delay in transmission.

(2) 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). Annex 1 provides guidance on the classification of the urgency of the recall of defective medicinal products.

Art. 10. - Class I defects are potentially life threatening. A rapid alert notification must be sent to all Member States of the EU, CADREAC countries, PIC/S, EDQM and MRA partners, irrespective of whether or not the batch was exported to that country.

Art. 11. – (1) Class II defects could cause illness or mistreatment, but are not Class I. A rapid alert notification should be sent only to those Member States, CADREAC countries, PIC/S, EDQM and MRA partners to which it is known, or believed, that the batch has been distributed.

(2) In identifying those countries, due consideration should be given to parallel distribution and import arrangements and the free trade between wholesale distributors within the EEA. In the case of parallel imports where there is difficulty in establishing the traceability of batches, consideration should be given to notifying all Member States through the Rapid Alert System.

Art. 12. - Class III defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons; these are not notified through the Rapid Alert System.

Art. 13. - 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 authorisation.

### CHAPTER IV

#### **Issue of a rapid alert notification**

##### **IV.1. Responsibility**

Art. 14. - 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. MRA partners identified by the manufacturer or importer as countries to which the defective batch was distributed should also be notified through the rapid alert system.

Art. 15. – (1) 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 a rapid alert (the issuing authority); the alert should include a recommendation on proposed action for all affected authorities.

(2) When time allows, the issuing authority should, as part of the investigation, come to an agreement on the content of the proposed action with the supervisory authority, the EMEA and the Committee for Human Medicinal Products (CHMP) 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.

(3) When, due to the urgency of the defect there is not sufficient time to develop a harmonized 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 through the rapid alert channel when ready (see point 21 in Annex 2 "Proposed Action").

Art. 16. - In the case of parallel distribution of a centrally authorised product and where no repackaging is carried out, the procedure described under Art. 15 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.

Art. 17. - 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, notifying MRA partners as appropriate. The Competent Authority should also notify the Supervisory Authority of the Member State in which the batch was manufactured or repackaged depending on the nature of the defect.

#### **IV.2. Format of the rapid alert and its transmission**

Art. 18. – (1) A suitable format for the notification of quality defects by the Rapid Alert System is given in Annex 2.

(2) The form should be completed clearly and (preferably) in English. It should be attached to a distribution list and the documents sent by fax or electronic mail where relevant, to the persons nominated in the EMEA rapid alert list, which includes working hours and out-of-hours contact names and numbers. Changes to contact names and/or numbers must be notified to EMEA so that the list can be updated as necessary.

(3) The rapid alert should be given a 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 second correspondence regarding this rapid alert).

(4) In the case of a Class I defect which must be notified out of hours, it may be necessary to use the out-of-hours contact telephone numbers in addition to the rapid alert.

Art. 19. – (1) Transmission of a Class I rapid alert must be concurrent with the national action.

(2) 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.

(3) When an authority issues a further rapid alert for a batch, point 18 in Annex 2 “Detail of Defect/Reason for recall” should begin with the text: “Rapid Alert following original rapid alert #ref.no.#”.

#### **IV.3. Action on receiving a notification under the Rapid Alert System:**

Art. 20. - The NMA should have a written procedure for the receipt and handling of rapid alerts from other authorities during and outside working hours. Unless it can be established unequivocally that the defective batch in question has not been distributed in the Member State (including parallel imports) the NMA should apply its national procedure for ensuring recipients of the batch are alerted. The class and urgency of the withdrawal should correspond to those of the initial rapid alert.

#### **VI.4. Fraud and Counterfeit Products**

Art. 21 – (1) The Rapid Alert System should be used to notify EEA Member States and MRA partners of the possible presence in the distribution network of counterfeit products, of those resulting from fraud in manufacture, packaging, distribution or promotion and products containing counterfeit starting materials.

(2) 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 a rapid alert notification 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/Reason for Recall” to enable it to be identified. Notification should be sent to the parties as indicated in section 3.2 for a class 1 defect and concurrently to EMEA.

#### **VI.5. Follow-up action**

Art. 22. – (1) The NMA 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.

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

(3) 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.

#### **VI.6. Annexes**

##### **VI.6.1. Annex 1: Classification of Quality Defects**

VI.6.2. Annex 2: Format for Rapid Alert Notification of a Quality Defect  
VI.6.3. Anexa 3: Format for Follow-up and non-urgent information for Quality Defects.

## ANNEX 1

### **Rapid Alert System:**

#### **Classification of quality defects of medicinal products, which establishes the urgency of the withdrawal**

**Class I.** Defects that are potentially life threatening, which could cause a serious risk to health. These defects must always be notified through the Rapid Alert System.

Examples:

- labelling a medicinal product with the label of another medicinal product;
- strength of the active substance non-compliant with the strength mentioned on the leaflet, with serious medical consequences;
- microbial contamination of an injectable or ophthalmic medicinal product;
- Chemical contamination with serious medical consequences;
- Mix-up of a medicinal product with another, when more than one container involved;
- Mix-up of a wrong active substance in a multi-component medicinal product, with serious medical consequences.

**Class II.** Defects which could cause illness or mistreatment, but are not Class I. These defects should be notified through the Rapid Alert System only to Member States, CADREAC countries, PIC/S, EDQM and MRA partners to which it is likely or known that the batch has been distributed.

Examples:

- Mislabelling of a medicinal product, e.g. wrong or missing text or figures;
- Missing or incorrect information on the leaflet;
- Microbial contamination of a non-injectable, non-ophthalmic sterile medicinal product with serious medical consequences;
- Chemical/physical contamination (significant impurities, cross-contamination, particulates);
- Mix up of products in containers;
- medicinal product which is non-compliant with its specification (e.g. dosage, stability, fill/weight);
- Insecure closure with serious medical consequences (e.g. cytotoxics, products for paediatric use, potent products).

**Class III.** Defects which may not pose a significant hazard to health, but whose withdrawal may have been initiated for other reasons.

Examples:

- Faulty packaging (e.g. wrong or missing batch number and/or expiry date);
- Faulty closure;

- Microbial contamination of a medicinal product with non-pathogenic microorganisms, which surpasses the admissibility limit imposed by technical specification;

ANNEX 2

**IMPORTANT - DELIVER IMMEDIATELY**  
**Rapid Alert Notification of a Quality Defect/Recall**

[add title in national language if necessary]	
[add letter head of sender]	
[turn into bilingual model as required].	
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/Lot Number:	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 released the batch in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC if different.

*This is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorised to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorised. If you have received this document in error, please notify us by telephone immediately and return it to us at the above address by mail. Thank you*

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### ANNEX 3

#### **Follow-up and non-urgent Information for Quality Defects**

[add title in national language if necessary]	
[add letter head of sender]	
[turn into bilingual model as required].	
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:	



14 Marketing Authorisation holder:		
15 Manufacturer <sup>1</sup> :	16 Contact Person:	
17 Subject title <i>Add bulk message here</i>		
22 From (issuing Authority):	23 Contact person:	
24 Signed:	2 Date: 5	26 Time:

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<sup>1</sup> 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 released the batch in accordance with Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC, if different