DECISION

No. 9/09.03.2007

on approval of Guideline on handling of reports of suspected quality defects in medicinal products

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, 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 Guideline on handling of reports of suspected quality defects in medicinal products is approved, according to the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on handling of reports of suspected quality defects in medicinal products

CHAPTER I
Scope

Art. 1. – (1) This Guideline is a translation into Romanian and an adaptation of Guideline EMEA/INS/GMP/313507/2006 on handling of reports of suspected quality defects in medicinal products, issued by the European Medicines Agency (EMEA).

(2) This Guideline was written 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 Guideline refers to the handling of medicinal products for human use, submitted to the National Medicines Agency (NMA) before, if necessary, a Rapid Alert is transmitted.

(2) This Guideline describes the elements of a procedure for receiving, assessing and categorising reports of quality suspected defective products that necessarily precedes a Rapid Alert.

CHAPTER II
Introduction

Art. 3. - Discussion at the Inspectors' Working Group and elsewhere has indicated the need to harmonise the handling of reports of suspected quality defects in medicinal products and confirm mutual confidence in member states' procedures for assessing the need to transmit a Rapid Alert of a quality defect.

Art. 4. – (1) Marketing Authorisation Holders under Art. 748 of Law 95/2006 on healthcare reform, title XVII – The medicinal product (i.e. manufacturers and importers of medicinal products) are obliged under Article 38 of Minister of Public Health Order No. 905/2006 on approval of principles and Guidelines of Good Manufacturing Practice for medicinal products for human use, including investigational medicinal products and according to point 8.8 from the Guideline on Good Manufacturing Practice approved through the NMA Scientific Council Decision No. 38/2006 to report to the NMA any defect in a medicinal product handled under their authorisation that could result in a recall or restriction in supply; it is normally the Qualified Person who has this responsibility.

(2) Reports of suspected defects may also be sent to the NMA by health professionals, wholesale dealers and members of the general public; in addition, a report of an adverse drug reaction may in fact be due to a defect in the quality of the product concerned.

Art. 5. - The NMA is obliged to take all appropriate measures to ensure that a medicinal products is withdrawn from the market if it proves to be harmful under normal conditions of use, if its composition is not as declared or if the control on the finished product or during the manufacturing process or other requirements of the manufacturing authorisation have not been fulfilled (Art. 829 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product).

Art. 6. - It is normally the responsibility of the company to recall a batch and to notify customers accordingly; it is normally the responsibility of the NMA to notify other authorities of the recall. The responsibility for notifying health professionals, media and the general public belongs to the company, as well as to the NMA.

CHAPTER III
Definitions

Art. 7. – Given this procedure, the following terms are defined as follows:

1. Suspected defective product - a medicinal product about which a report has been received suggesting that it is not of the correct quality, as defined by its Marketing Authorisation;

2. Batch recall - the action of withdrawing a batch from the distribution chain and users; a batch recall may be partial, if the batch is only withdrawn from selected distributors or users;

3. Rapid Alert - an urgent notification from one competent authority to other authorities that a batch recall has been instituted in the country originating the rapid alert; the procedure for issuing rapid alerts is defined in the NMA Scientific Council Decision No. 8/09.03.2007, concerning the approval of the procedure for handling Rapid Alerts and recalls arising from quality defects.

CHAPTER IV
Handling process

IV.1. Process aim

Art. 8. - The process aim consists of recording and assessing, during and outside office hours, reports of suspected defective products and to implement action with appropriate urgency.

IV.2. Process steps

Art. 9. – (1) NMA contact details for reporting suspected defective medicinal products should be made widely known and readily available to those likely to need to make a report; this would include manufacturers and marketing authorisation holders and may also include wholesalers, hospitals, pharmacists, veterinary practitioners and local health authorities.

(2) A dedicated, continuously manned telephone line is preferred; arrangements should be made to divert calls if necessary during out-of-office hours. If other means such as fax or e-mail are used they should be monitored frequently, including during out-of-office hours.

Art. 10. - Every contact should be recorded, using a standard format for recording information. The first informant is unlikely to have all the required information so it is most important that a contact is agreed from whom further information may be obtained. A registered file should be established for each suspected defect to collect information as it becomes available.

Art. 11. - The report should be referred with minimum delay to a person(s) able to make an initial professional assessment of the nature, extent and urgency of possible public health risk. A target time should be set for reports to be referred to this person, normally less than one hour. It may be possible to give guidance to the person receiving out-of-hours

reports on the nature of reports which must be relayed to the professional assessor before the next routine working day.

Art. 12. - The initial professional assessment should include the following considerations:

- risk to health of an individual if the suspected defect is real (consider risk to vulnerable patients as well as normal individuals, risk of not receiving the correct medication, risk from incorrect dosage, long-term risk as well as immediate risk (e.g. if a complete dispensed container is faulty the impact on the individual will be cumulative);
- probability that the defect is real and occurs in the medicinal product supplied by the manufacturer (e.g. not a clinical effect with a different cause, not a defect introduced at the time of dispensing);
- in the case of risk of distorting the analysis in national programmes against certain viral diseases, in case of suspicion of defective vaccines (cross contamination with a virus).

Art. 13. - At this stage it will be decided whether the potential hazard to health is such that extraordinary measures must be taken (including the convening of an emergency action group out-of-office hours) or whether further consideration may be left for normal office hours.

Art. 14. - Further professional assessment of the risk from the product should involve discussion with the manufacturer and include consideration of:

- any other reports which may be related;
- the distribution of the batch (e.g. restricted to known hospitals, widespread through wholesalers);
- date of first and last distribution;
- any remaining stock with the manufacturer;
- probability that other batches are affected in the same way, and their distribution.

Art. 15. - If a recall is being considered, extremely important issues to consider include:

- possibility of an out-of stock situation;
- availability of alternative products;
- efectul clinic al unei întreruperi în furnizare.
- clinical effect of a disruption in supply.

Note: *No supply of a product may be worse than use of product with a suspected deficiency.*

Art. 16. – (1) Direct personal contacts are important, especially with the person making the report, the person co-ordinating action for the company (usually the Qualified Person), the inspector familiar with the manufacturer and persons responsible for vigilance within the NMA.

(2) It is often helpful in detailed discussions if communication is between professional equivalents, e.g. medical assessor with medical staff of the company, inspectors with Qualified Person(s) or production staff, analytical assessors with Quality Control staff, etc.

(3) All information obtained verbally should be confirmed in writing.

IV.3. Samples

Art. 17. - Wherever possible the sample involved in the defect report should be obtained by the NMA. It should normally be examined by an Official Medicines Control Laboratory of the NMA. In certain cases samples should be provided to the company for

examination under full supervision of the NMA. Results should always be made available to the company.

***Note**: A company should have instructions for release of retained samples in order not to have all of them used up during an emergency situation other than with consent from the NMA.*

IV.4. Inspection

Art. 18 – (1) The inspector who knows the manufacturing site should be made aware of the report; he/she may comment on general GMP compliance and what related products made. On-site inspection may be required to assess batch records of the product concerned, plant records and records of other batches of products which could also be affected.

(2) Samples may be taken of the batch concerned, related batches and related starting materials.

(3) When considering taking material from the company's retained samples, consideration must be given to the quantity available and all tests which may be required for further investigations. These may be prescribed by the marketing authorisation and/or national requirements.

IV.5. Preparing a Decision

Art. 19. – (1) Having considered all the available information, including the need to make a decision without waiting for full information to be available because of the potential risk to public health, a decision will be taken on immediate appropriate action, which may be one or more of the following according to national procedure:

- filing without follow-up;
- further investigation;
- quarantine of remaining stock at manufacturer and quarantine or recall at wholesalers either while further investigations occur or to prevent further distribution even if a full recall is not required;
- Good Manufacturing Practice measures to avoid a defect recurrence;
- distribution of a "caution in use" notice to concerned health professionals;
- notification of the batch recall to selected health professionals (e.g. particular hospitals, clinics, dentists);
- notification of the batch recall to all health professionals (e.g. including all hospitals, doctors, pharmacies);
- notification of the batch recall through the media;
- publication on the NMA website, in the Informative Bulletin or similar;
- an assessment should be made if other batches of the same product or other products could be affected by the same GMP deficiency.

(2) The exact wording of any notification should be checked and if possible agreed with the company. Particular attention should be paid to check the batch number(s), expiry dates, product name and strength. Advice should be given on where further information may be obtained (normally from the company).

(3) The distribution of the notification to interested parties within the authorities should be agreed. This may include national Ministers and other government departments, government press officers and, by means of a Rapid Alert, authorities and organisations in other countries (EU/EEA, MRA Partners, PIC/S, WHO, others).

(4) As far as possible standard formats, wording and distribution lists should be used for the notifications with the aim of ease of understanding by the recipient and lack of ambiguity.

IV.6. Validating the decision

Art. 20. - According to the NMA procedures, proposed approval should be approved by the highest level of management.

IV.7. Implementing the Decision

Art. 21. - The decision shall be implemented in compliance with national procedures and the EU Rapid Alert Procedure.

IV.8. Follow-up

Art. 22. - There should be consideration of what and if any action to take concerning the Marketing or Manufacturing Authorisations and their holders is necessary.

Art. 23. - The PID should asses the follow-up actions taken by the company, including the reconciliation of issued, returned and remaining stocks, the investigation into the cause of the defect and actions to prevent a repetition.

Art. 24. - Completion of any follow-up actions should be checked, for example completing and organising records and archiving according to national procedure.

CHAPTER V
Quality Assurance

Art. 25. - All procedures should be documented and maintained up to date.

Art. 26. - Contact lists for officials and companies should be maintained up-to-date and should be verified at intervals (e.g. a rolling programme of annual checks of company contacts, possibly as part of Good Manufacturing Practice inspections).

Art. 27. - All staff who could be involved in receiving a report of a suspected defective product or handling a Rapid Alert should be trained in the relevant procedures and have access to a copy of the SOP and report form wherever they may be required to act (including at home if they are on call outside-office hours).

Art. 28. - It is particularly important that those procedures which may need to be followed by staff not routinely involved (e.g. called upon as a reserve) and/or required to be involved when away from their office should be detailed and easy to follow.