DECISION

No. 25/28.09.2007

on approval of Guideline on
Rapid Alert and non-urgent information system in pharmacovigilance

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order no. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 28.09.2007, 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 Rapid Alert and non-urgent information system in pharmacovigilance 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 Rapid Alert and non-urgent information system in pharmacovigilance

CHAPTER I
General principles

Art. 1. – This Guideline is a translation into Romanian and an adaptation of section 4 – Part II – of Eudralex, Volume 9a - PHARMACOVIGILANCE.

CHAPTER II
Introduction

Art. 2. - (1) During the marketing period of a medicinal product urgent measures to safeguard public health may be necessary.

(2) Within the European system of pharmacovigilance it is essential that information concerning safety hazards possibly resulting in major changes to the marketing authorisation status or withdrawal of a product, is exchanged between the Member States, the European Medicines Agency (EMEA) and the European Commission (EC) in the case of centrally authorised medicinal products with the appropriate degree of urgency.

Art. 3. - (1) Generally, any safety issue identified by a Member State after the evaluation of available data in that State, or any other relevant important information received by that Member State, should be transmitted to the other Member States (MS), EMEA and EC.

(2) This approach also includes any action initiated by the Marketing Authorisation Holder (MAH).

Art. 4. - An early exchange of information will enable the Competent Authorities (CAs) to initiate data research and seek specialist expertise so that necessary decisions may be taken as soon as possible and in a coordinator manner.

Art. 5. - (1) In view of supporting the rapid notification of safety issues and exchange of information in view of taking appropriate measures, the Competent Authorities of the MS, EMEA and EC have started a rapid alert system and non-urgent information, in accordance with the procedure describe in this Guideline.

(2) In order to avoid the effort's multiplication and to ensure a more efficient use of the national systems' resources, in view of supporting the unofficial communication between MSs (pre-signal information exchange), the information received during signal's detection phase may be transmitted as well.

(3) The MAH should be properly informed about suspected signals which are considered to require additional analyses.

Art. 6. – (1) The purpose of a rapid alert (RA) is to inform, by an appropriate emergency degree, the CA, EMEA and EC concerning pharmacovigilance data concerning a medicinal product, indicating the fact that urgent measures to protect public health may be needed.

(2) It is mandatory that these issues are communicated at an early stage, usually before making a decisionin a MS.

Art. 7. – The RA may be used by the MS and in view of informing the CAs in other MSs, the EC and the EMEA, in accordance with Art. 107 (1) and (2) and Art. 36 (2) of Directive 2001/83/EC and Art. 20 (4) of Regulation (EC) No. 726/2004.

Art. 8. – According to Art. 107(1), the involved MS should inform the MAH.

Art. 9. – (1) The RA system must not be used for the exchange of less important information.

(2) In this purpose, the non-urgent information (NUIS) system must be used.

Art. 10. – The NUI system is also used to gather the exchange of information between the CA and the EMEA which do not meet the requirements of an AR.

Art. 11. – An RA or NUI may be initiated by the EMEA.

Art. 12. – Subsequent to the launch of an RA or NUIS, the safety issue may be reassessed as follows:

a) At the level of the Pharmacovigilance Working Group (PhVWP), based on the Medicinal Product's Monitor and an evaluation report, if needed; or

b) at the level of the Committee for Human Medicinal Products (CHMP); or

c) within the procedures specified in Art. 31, 36 and 37 or Art. 107(2) of Directive 2001/83/EC or Art. 20 of Regulation (EC) No. 726/2004.

Art. 13. – RA/NUI should be used mainly to highlight the issues related to the medicinal product's risk-benefit assessment, in accordance with Directive 2001/83/EC or Regulation (EC) No. 726/2004.

Art. 14. – In case of safety issues of products which were not authorised as medicinal products (e.g., chemicals), this system may be used dacă if the information provided is relevant for the medicinal products concerned.

Art. 15. – Occasionally, in view of preparing the discourses at the PhVWP level, a NUI may be transmitted in view of soliciting information about the national policies, viewpoints on guideline projects or certain organisational issues.

Art. 16. – RA/NUI may also be used to grant information about major findings of pharmacovigilance inspections.

Art. 17 – (1) RA concerning the quality issues of medicinal products/specific series are not included in this Guideline; recommendations for these aspects are mentioned in „Compilation of Community Procedures relating to inspections and information exchange".

(2) However, in case of an adverse reaction, lack of efficacy or suspected lack of efficacy, associated to some quality issues, the cooperation with the inspectorate should be initiated in order to analyse the implications of the quality issue upon safety.

CHAPTER III

Criteria for the use of information exchange methods concerning the safety issues of medicinal products

III.1. Rapid Alert (RA)

Art. 18. – RA shall be used when an MS identifies a safety issue which has a potential major impact upon the known risk-benefit assessment of the medicinal product and which could justify undertaking prompt regulatory actions and communication sent to the medical staff and the general public, such as:

a) urgent safety restriction, suspension, recall or withdrawal of the MA and/or the medicinal product's market withdrawal;

b) suspension of the marketing and/or suspension of the use of the medicinal product;

c) actions concerning the medicinal products derived from human blood and human plasma, subsequent to the appearance of the Creutzfeldt – Jacob disease (vCJD) in the donor's blood (specifying the marketing series as well as the expired series);

d) important modifications in the Summary of product Characteristics (SPC), such as:

- introduction of new contraindications;
- introduction of new warnings;
- reduction in the recommended dose;
- restrictions of the indications;
- restrictions on the availability of the medicinal product.

e) the need of expedited informing of the medical staff or patients relating to any identified risk.

Art. 19. – In accordance with Art. 107(1) of Directive 2001/83/EC, RA should be used to inform the MS, EMEA and EC on an expedited basis when, following the assessment of pharmacovigilance data concerning a medicinal product authorised through the national procedure, an MS considers the MA withdrawal or recall or variation via SPC necessary, as previously mentioned.

Art. 20. – In accordance with Art. 107(2) of Directive 2001/83/EC, in case a MS suspends an MA for an authorised medicinal product via national procedure in view of the protection on an expedited basis of public health on its territory, the MS should forward an RA no later than one working day as of recall, while inforing the CAs of the MS, EMEA and EC.

Art. 21. – If, in view of an urgent public health protection, an MS suspends on its territory the use and marketing of a medicinal product authorised through the mutual recognition or decentralised procedure, then an RA no later than one working day after suspending that product, exposing the reasons for that action and therefore informing other MSs, the EC and EMEA in accordance with the legal requirements of

Art. 107 and 36(2) of Directive 2001/83/EC.

Art. 22. – (1) In case of medicinal product authorised throughg the centralised procedure, if the initiation of an urgent measure is consider essential for protecting the human health or environment, the MS may suspend the use of a medicinal product on its territory in accrodance with Art. 20(4) al Regulation (EC) No. 726/2004.

(2) In such cases, the MS should immediately inform the EC and EMEA, no later than the last working day, also providing the reasons for this action.

(3) In these cases and in view of meeting the legal solicitations, the MS should transmit an AR, while informing the EC, EMEA and the other MSs.

Art. 23. – In case of using RA relating to human blood/plasma-derived medicinal products, in order to notify the occurence of vCJD in the donor's blood, in addition to the Official Medicines Control Laboratories (OMCL) and, if the series withdrawal is necessary, compared to the Rapid Alert of the Inspection (see „Compilation on community procedures on inspections and exchange of information"), the RA system in pharmacovigilance shall be used.

Art. 24. – In addition to the aforementioned criteria, RA may also be used when there are concerns relating to the modification of the risk-benefit assessment of the medicinal product or of an active substance, as follows:

a) the existence of a report series (or sometimes of a single thoroughly documented case) of an unexpected adverse reaction;

b) reports on an expected adverse reaction, suggesting a higher gravity or longer-term sequelae than those previously encountered, or which identify the new risk factors;

c) a significant increase in the reporting rate of an expected adverse reaction;

d) evidence issued from studies (clinical or non-interventional studies), which point out an unexpected risk or modification of the frequency or gravity of a known risk;

e) data attesting that the medicinal product's efficacy is not compliant with its attributed efficacy;

f) evidence attesting that the risks involved by a medicinal product are higher than the alternatives with similar risks.

III. 2 Non urgent information (NUI)

Art. 25. – (1) NUI must be used for the exchange of information related to safety issues which do not meet the criteria concerning the launch of an AR, as it was previously defined.

(2) For instance, the NUI should be used to communicate pharmacovigilance data which do not require immediate measures or emergencies and/or if additional information is solicited by another MS, in view of supporting that issue's assessment.

Art. 26. – In each case, the reason for NUI transmission must be specified:

a) provision at an early stage of published pharmacovigilance information;

b) information about a new potential safety signal;

c) information about the status of the implementation of regulatory actions;

d) information which may be useful for other MSs but which do not require an answer (e.g. withdrawal of a medicinal product out of other reasons than safety reasons, the outcome of discussions from the safety committees at national level, the case when an assessment report relating to other subjects, press surveys, direct communication with the medical staff, current media activity);

e) request of information;

f) organisational issues;

g) easing data collection in view of external parties interaction.

CHAPTER IV
Procedures

IV.1 Transmission of the RA or NUI

Art. 27. – (1) In accordance with Art. 26 of Regulation No. 726/2004 and Art. 105 of Directive 2001/83/EC, EMEA, in partnership with MS and EC, has founded a data processing network in view of the rapid share of information between the CAs in case of an alert relating to a manufacturing defect which leads to adverse reactions, serious adverse reactions and other pharmacovigilance information relating to medicinal products placed on the market within the EU.

(2) RA and NUI belong to another category of pharmacovigilance data and use EudraNet as a data processing network.

Art. 28. – (1) In order to transmit RA or NUI, the EudraNet postal box shall be used for RA, (address list „All Human RA"), which addresses to all CA, MS, EMEA and EC contact points.

(2) The latest EudraNet e-mail policy adopted shall be appropriately used.

Art. 29. – (1) Following the successful implementation of the electronic transmission between the EMEA, MS and EC, this replaced the fax, system once used in the exchange of such information.

(2) However, in case of emergency, such as the impossibility to access the EudraNet or the existence of a network defect, the ex-transmission system via fax should be mentioned and used as an alternative.

(3) Changes in fax numbers must be immediately notified to the EMEA, EC as well as to the contact points of the MS.

(4) EMEA and all CAs should own a fax for the RA and NUI systems, to allow the storage of fax numbers and contacting the group.

Art. 30. – The electronic communication with partners who are not connected via the EudraNet, such as MAHs and WHO, should be conducted in a way which guarantees safety and privacy of the data submitted, such as via the EudraLink.

Art. 31. - (1) Models of RA and NUI are attached (see Annex 5.3.1 and 5.3.2).

(2) These models are also available on the EudraNet website (http://www.eudra.org/eudraportal) and may be accessed via the established pharmacovigilance domain.

Art. 32. – (1) In view of transmitting an RA or INU, the chosen model (see Annexes 5.3.1 and 5.3.2) should correspond to the criteria for RA or NUI.

(2) The provided information relating to the safety issue and the reasons for the RA and NUI transmission should be clear and concise, so that the first transmission does not require any clarifications.

(3) In order to attain this objective, the following rules should be followed:

a) the involved medical product(s) should be identified by the INN and, when it is available and relevant, by its strength, forms and INN numbers;

b) the status of the medicinal product's marketing authorisation should be specified, e.g. if it is authorised through centralised, national, mutual recognition, decentralised, "arbitrary" procedures, or the nature of that medicinal product, if not authorised;

c) The CA which initiates the RA/NUI should transmit at least the minimum of information mentioned in the table at the end of this Guideline and should employ the attached models (see Annex 5.3.1 and 5.3.2 of Eudralex, Volume 9a - PHARMACOVIGILANCE);

d) any information required by the addressee should be clearly specified, along with the deadlines;

e) where required, the RA/NUI annexes should also be submitted in elctronic format; the format which must be used for the electronic transmission is the one specified in the last version adopted by the EudraNet email policy; if the annexes are not available in electronic format, the RA/NUI model should be filled in, mentioning that the annexes shall be separately submitted by fax; this should be sent to the addresses mentioned in the defined list, to the appointed PO boxes; a copy of the completed form shall be attached to the annexes sent by fax;

f) RA/NUI should be transmitted to the contact points nominated by the EMEA MSs, to the CHMP president and the EC. In case of medicinal products authorised through centralised procedure, RA/NUI should also be transmitted to the rapporteur; if the transmission system consists of sending information via fax, RA/NUI shall be transmitted to the contact points mentioned above;

g) the e-mail's title containing the completed model should:

- identify the medicinal product(s) involved in the INN, the name of the medicinal product's class or other adequate name;

- provide a key word in order to identify the safety issue or other reason for the transmission of the RA or NUI, using the common abbreviations (e.g. „GItox" for gastrointestinal toxicity);

- identify the nature of the message – whether it is RA or NUI;

- specify a deadline, if required.

The title of the e-mail would look like this: „INN – GI tox – RA" or „INN – Eyedisorder – NUI – per dd/mm/yy".

h) in case of emergency, if the interested MS has suspended a medicinal product's MA or withdrawn the medicinal product from the market in order to protect public health, the EMEA, EC and all CAs of the MS should be informed no later than the following working day;

i) when a rapid alert is transmitted, the involved CAs and their duties depend of the type of procedure which led to the marketing authorisation of that medicinal product:

- in case of medicinal products authorised through national procedure, the initiating MS should adequately and promptly inform the MAHs from that country, in view of initiating research and exchange of information; The recipient MS is responsible for informing the MAH from that country;

- in case of medicinal products authorised through mutual recognition/decentralised procedure, RMS should adequately and promptly inform the MAH;

- in case of medicinal products authorised through centralised procedure, EMEA, in agreement with the rapporteur, shall promptly initiate a research and an exchange of information;

- the initiator should establish whether the RA meets the notification criteria of WHO in accordance with Chapter II.6 of Eudralex, Volume 9a - PHARMACOVIGILANCE.

j) RA could be used in order to prepare and apply an urgent restriction out of safety reasons in accordance with the recommendations of post-authorisation procedures for medicinal products autorised through centralised procedure (see CHMP recommendations for medicinal products for human use in the post-authorisation period; for medicinal products authorised through mutual recognition and decentralised procedure, see the MS standard operating procedure for the safety emergency restriction).

IV.2. Answers to the RA/NUI

Art. 33. - (1) Unless otherwise specified, the answers to the RA should be sent to all MSs, the EMEA and the EC no later than one week after having received the AR.

(2) The initiator of an RA which requires information should comply the RA answers and send them to all MSs, EC and EMEA, as soon as possible.

Art. 34. – (1) In case of a NUI, the sollicited answers should be provided to an initiating AC and the EMEA within the time frame mentioned by the initiator, unless otherwise specified.

(2) The document containing all NUI-related answers should be transmitted by the NUI initiator to all MSs, EC and EMEA.

Art. 35. – The RA/NUI should include the original RA/NUI and all the answers received from the MS.

Art. 36. – (1) The title of the e-mail message which contains the complete answer should indicate whether the answer to RA or NUI is concerned (such as „INN-GI tox RA Response")

(2) The RA or NUI answer should refer to the original message (the sender's name, date of the original message, reference of the alert).

Art. 37. – The information required by the RA/NUI initiator shall be submitted.

Art. 38. – EMEA resumes the issues brought by RA and NUI in the Medicinal Products Monitor, which is discussed and updated at each PhVWP meeting.

IV.3 Evaluation of the Rapid Alert

Art. 39. – After transmitting an initial RA, an interim assessment report should be edited for the following meeting of the PhVWP:

a) in case of a medicinal product authorised through national procedure, the initiating MS edits the assessment report related to the risk-benefit balance, taking into account all information, including those received and collected by the other MSs;

b) in case of a medicinal product authorised through mutual recognition/decentralised procedure, the risk assessment is usually conducted by the RMS, except when other agreements have been established between the MSs; in each case, there should be an agreement concerning the RA management responsibility and the assessment report relating to the risk-benefit assessment, belonging to the RMS, interested MS or represent a common responsibility;

c) in case of a centrally authorised medicinal products, the reporter should work in close contact with the RA initiator in view of assessing the safety issue; in each case, there should be an agreement relating to the responsability of submitting an assessment report on the risk-benefit assessment, which belongs to the rapporteur, the initiator MS or represents a common task.

Art. 40. – When the collected information provides evidence of a serious safety issue, a complete assessment report should be edited concerning the risk-benefit assessment, which shall be sent to the PhVWP, for analysis.

Art. 41. – The assessment report should be transmitted to all CAs in the MSs, EMEA, EC and MAHs and should be discussed during the following meeting of the PhVWP.

Art. 42. – The assessment report should be transmitted electronically, via the EudraNet PhV post office box (list of the „All Human Pharmacovigilance" address) as mentioned in the latest adopted version of the EudraNet e-mail policy.

Art. 43. – It should be established wether the issue represents a community interest and Art. 31, 36 or 37 of Directive 2001/83/EC should be referred to (see Chapter II.5 of Eudralex, Volume 9a - PHARMACOVIGILANCE).

IV.4 Assessment of the NUI

Art. 44. – (1) According to the Medicinal Products Monitor, PhVWP discusses all the subjects which have undergone an exchange of information as a NUI; the processing style of the safety issue shall be established on a case-by-case basis.

(2) In case an assessment report is considered necessary, the same evaluation procedure as for the RA shall be applied (see CHAPTER II.4, section 3.3 of Eudralex, Volume 9a - PHARMACOVIGILANCE).

Minimum of information required for the RA/NUI transmission

1. Identification
- type of message - reference document - from: - to: - date of message
2. Medicinal product - active substance(s) according to their INN (plus name of the class, if needed) - invented name - marketing authorisation procedure for the medicinal product: □ medicinal product authorised via centralised procedure □ medicinal product authorised via mutual recognition procedure □ medicinal product authorised via decentralised procedure □ medicinal product authorised via national procedure □ medicinal product wich has been the subject of an „arbitrary" procedure - pharmaceutical form and dosage (if appropriate) - Marketing Authorisation Holder - manufacturer (if essential)
3. RA/NUI Reason
4. Action(s)
- action(s) proposed - action(s) taken (steps taken to collect more information at a national level and temporary steps taken to protect the Public Health)
5. Information exchange
- information required