RAPID ALERT SYSTEM (RAS) IN PHARMACOVIGILANCE

Guideline Title	**Rapid Alert System (RAS) in Pharmacovigilance**
Legislative basis	**Directive 65/65/EEC as amended, Council Regulation 2309/93**
Date of first adoption	**July 1991** **This version adopted June 1996**
Date of entry into force	**Immediate**
Status	**Last revised 1996**
Previous titles/other references	**Rapid Alert System / III/3917/90**
Additional Notes	**This guideline describes the Rapid Alert System (RAS) run by the competent authorities of the Member States in order to facilitate early exchange of information concerning possible safety hazards relating to marketing medicinal products between the Member States, the Commission and the Agency. It replaces the previous 1991 version.**

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INTRODUCTION

During the marketing period of a medicinal product urgent measures to safeguard public health may be necessary. 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 Commission and the Agency in the case of centrally authorised medicinal products with the appropriate degree of urgency.

An early exchange of information will enable the competent authorities to initiate data research and seek specialist expertise so that necessary decisions may be taken as soon as possible. Therefore the competent authorities of the Member States run the Rapid Alert System (RAS) in accordance with the procedure laid down in this guideline.

PURPOSE

The RAS alerts other Member States, the Commission and, in the case of centrally authorised medicinal products, the Agency with the appropriate degree of urgency, to pharmacovigilance data for medicinal products which indicate that action could be needed urgently to protect public health. It is essential that communication of such problems occurs at an early stage, normally before a decision is taken in a Member State.

The issue may be discussed then in a broad manner

- in the Working Party on Pharmacovigilance on the basis of an assessment report,
- in the CPMP

or formalised within procedures laid down in Article 12 and 13 of Directive 75/319 as amended or Article 18 of Regulation 2309/93.

SCOPE

The RAS should be used in problems relating primarily to safety of medicinal products authorised according to Directive 65/65 EEC and Regulation 2309/93. The system must not be saturated by the transmission of less urgent information. The Infofax-system should be used to transmit less urgent problems.

Rapid alerts regarding quality problems or concerning special batches of a medicinal product are not considered in this guideline. Those Rapid Alerts must be handled as laid down in the document III/5698/94-EN *Compilation of Community procedures on administrative collaboration and harmonisation of inspection*, worked out by the Working Party on Control of Medicines and Inspections in 1994 or further updates.

CRITERIA

The RAS should be used when a Member State has concern about a change in the balance between risks and benefits of a medicinal product and therefore major changes in the status of approval seem to be necessary. A need to inform professionals or users about the identified risk without delay may be an additional reason for sending a rapid alert. Normally the case relating to the suspicion or concern is formulated by one Member State after evaluation of the data available in that Member State and any other relevant information available.

With regard to a certain medicinal product or active ingredient authorised according to the Directive 75/319 as amended or Regulation 2309/93 suspicion or concern may be based on:

- report(s) of unexpected and serious ADRs
- reports of an expected ADR which suggest greater severity or long-term sequelae than known or which identify new risk factors
- increase in the reporting rate of expected serious ADRs
- evidence from formal studies (clinical trials or epidemiological studies) indicative of unexpected risk or a change in frequency or severity of a known risk
- knowledge that the efficacy of a medicinal product is not established as assumed to date
- evidence that the risks of a particular product are greater than alternatives with similar efficacy.

Major changes in the authorisation status may be:

- recall of the drug from the market
- suspension or withdrawal of the marketing authorisation
- changes in the SPC, i.e. new contraindications, restriction of indications, reduction in dose or restriction in the availability of a medicinal product.

PROCEDURE

I. SENDING A RAPID ALERT

Presently the most efficient means to transmit this kind of information and available in all Member States is Telefax. Electronic transmission of information is being piloted between some Member States and will be the future mode of information exchange. The establishment of pre-defined data formats is essential to ensure collection of similar data, aid in exchange of information among the Member States, and assist common evaluation. Proposed forms are enclosed with this guideline.

If using the RAS the Member State should comply with the following rules:

a) The fax should be headed clearly as a RAPID ALERT at the top.

b) The fax should provide clear and concise information on the reasons for the Rapid Alert so that there is no need for clarification in the first instance.

c) The Member State generating the alert should transmit at least the minimal data listed in Annex I and form A.

d) Any information required from recipients should be specified clearly.

e) The fax should be preferably typewritten; the size of the letters should be large enough to ensure that the text is satisfactory readable.

f) Annexes to the fax form should be used if necessary to give sufficient details.

g) The fax should be transmitted to the contact points of the Member States, the Agency and to the Commission.

h) In case of urgency, when the Member State concerned has suspended the marketing authorisation of a medicinal product or withdrawn the drug from the market in order to protect human or animal health or the environment, the Agency and all Member States will be informed at the latest on the following working day.

I) The Member State generating a Rapid Alert should inform the MA holders concerned in his country adequately and promptly. Receiving Member States are responsible for informing MA holders in their own countries. Information of the MA holders may be given via associations of the MA holders both in sending or receiving Member States.

II. FOLLOW UP PROCEDURE

Responses from Member States

Responses to a specific Rapid Alert should be sent only to the originating Member State and the Agency not later than one week of receipt of the fax. The heading of these forms (see form B) should be “ANSWER TO RAPID ALERT”. The information requested by the generating Member State should be provided.

Assessment Report

The originating Member State should collate all information received from the Member States and prepare an interim assessment report within five weeks after transmission of the initial Rapid Alert to all Member States and the Agency. When the collated information provides evidence of a serious safety concern the originating Member State should prepare a full risk-benefit assessment report for consideration by the Pharmacovigilance Working Party. This should follow the form and content of the guideline on *Assessment Reports* (Annex II) and following the template (Annex III). This should be sent to all Member States, the Agency, and the Commission, and should be considered at the next meeting of the Pharmacovigilance Working Party. Consideration will need to be given to whether the matter is of Community interest and should be referred under Article 12 of Directive 75/319 as amended.

The Agency will collate the information and compile the basic data from the Rapid Alerts and will include conclusions in the “Drug Monitor Form”.

ANNEX I

Information for transmission of information about detected signals

MINIMAL DATA THAT SHOULD BE FILLED IN EVERY CASE

1. Identification:

- Type of message categories: Rapid Alert/Non-urgent Message
- Reference
- From:
- To:
- Date:

2. Drug(s)

- Brandname(s):
- Active substance(s): (INN, DCI)
- Pharmaceutical form and dosage (if appropriate):
- Marketing authorisation holder(s)
- Manufacturer (if essential)

3. Reason for Alert

- Source of information: Spontaneous reports/Post-Marketing Study/Clinical Trial/Pre-clinical Study
- Summarised evidence relevant to alert

4. Actions

- Action(s) proposed
- Action(s) taken (steps taken to collect more information at a national level and temporary steps taken to limit risks)

5. Information exchange

- Information required

ANNEX II

Pharmacovigilance Assessment Report

FORMAT AND CONTENT

I. Introduction

This section should clarify why the assessment has been undertaken.

II. Assessment of risks

This section will be specifically devoted to the safety concern under evaluation. It should encompass all relevant sources of information, including spontaneous reports, published literature, studies (pre-marketing clinical trials, postmarketing studies, epidemiological studies and intensive monitoring data), other data, e.g. mortality data to:

a) characterise the problem (nature, severity, outcome);

b) assess causal association;

c) estimate frequency and comparative frequency, where possible;

d) provide evidence of risk factors.

III. Assessment of benefits

It should take into account the following, where known:

a) the nature of the illnesses for which the medicine is indicated (e.g. fatal, life-threatening, disabling, self-limiting, etc.);

b) absolute efficacy, as judged by placebo-controlled clinical trials;

c) relative efficacy, as judged by studies comparing efficacy with that of appropriate alternative treatment(s);

d) the characteristics of the population exposed to the medicine (e.g. elderly and hospitalised, young and healthy, etc.).

IV. Overall risk-benefit evaluation

This section includes:

a) an overall benefit/risk analysis in the context of the safety problem under assessment and relevant comparative safety with other drugs in the same class or for the same therapeutic indication;

b) discussion of the options for improving the risk-benefit ratio;

c) recommended options for responding to the safety issue.