



Your date	Your reference	Our date	Our reference	Office/officer
		2005-10-13	200500002-5	LB/OV/HL

## **CIRCULAR 5/2005 – ELECTRONIC TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS.**

### **Background**

This circular outlines the requirements for electronic transmission of individual case safety reports (ICSRs) between Marketing Authorisation Holders (MAHs) and the Norwegian Medicines Agency (NoMA).

The NoMA has previously, in Circular 4/2003, informed the MAHs about the requirements for electronic transmission of ICSRs. Circular 4/2003 is replaced by Circular 5/2005.

Electronic transmission of ICSRs regarding medicinal products for veterinary use is beyond the scope of this Circular.

### **Requirements and authority**

In accordance with Regulation 726/2004, Directive 2001/83/EC and Norwegian regulations (*Forskrift om legemidler §11-2 b*), all ICSRs concerning medicinal products with a MA are to be transmitted electronically as from 20<sup>th</sup> November 2005. International (ICH E2B) and European standards and guidelines for electronic transmission have been published. As from 20<sup>th</sup> November 2005, the NoMA will only accept electronic transmission of ICSRs in accordance with the abovementioned standards. This includes both **sending and receiving** electronic ICSRs to/from MAHs, NoMA and the European Medicines Agency (EMA). As from this date all MAHs within the European Economic Area (EEA) are obliged to implement a system for electronic exchange of ICSRs in compliance with these standards.

The Norwegian Medicines Agency has since 2003 had in place a pharmacovigilance system which is in compliance with the requirements for electronic transmission of ICSRs.

*Letters should be addressed to the Norwegian Medicines Agency. Please state our reference*

**Alternative solutions for MAHs who are not able to send and receive electronic ICSRs in compliance with the abovementioned standards by 20<sup>th</sup> November 2005.**

MAHs, who have not implemented a system for electronic exchange of ICSR by 20<sup>th</sup> November 2005, are recommended to contact the EMEA in order to get access to their web-based pharmacovigilance database (WEB trader component of EVWEB) as an (interim) solution. EVWEB is specifically designed for Small and Medium Size MAHs. As an alternative solution, commercial service providers are also available. The NoMA does not have the capacity to offer alternative solutions.

**“Backlog”**

The Norwegian Medicines Agency will send out an information letter specifying the national requirements for the backlog (transmission of ICSRs from the period 1995-2005 to EudraVigilance) in early 2006.

**SUSARs**

Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur in interventional clinical trials should be transmitted electronically (E2B-format) to the Norwegian Medicines Agency (organisation-ID: “NOMACT”). SUSARs should also be sent electronically to the EMEA (EVCTM) in compliance with existing guidelines. Questions regarding electronic transmission of SUSARs should be directed to the Clinical trials section (e-mail: [klut@noma.no](mailto:klut@noma.no)).

**National Requirements**

Non-EEA reports:

The Norwegian Medicines Agency would prefer not to receive ICSRs originating from non-EEA countries. According to the current requirements, such reports should be sent electronically to the EMEA pharmacovigilance database (EudraVigilance) – where they will be available for the Norwegian Medicines Agency.

**NORWEGIAN MEDICINES AGENCY**

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Enclosed: “Exchange of adverse drug reaction reports between the Norwegian Medicines Agency and the Marketing Authorisation Holders.”



Attachment to Circular 5/2005

## Exchange of adverse drug reaction reports between the Norwegian Medicines Agency and the Marketing Authorisation Holders

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**Note:**

This document concerns post-marketing reports of adverse drug reactions. Suspected Unexpected Serious Adverse Reactions, SUSARs, arising from clinical trials are beyond the scope of this document.

### LEGISLATION

As part of the extended EEA-agreement, Norway is covered by the European legislation regarding medicinal products, including the pharmacovigilance regulations.

#### EU legislation

Regulation 2309/93

Regulation 540/95

Regulation 726/2004

Directive 2001/83/EC as amended by Directive 2002/98, 2003/63, 2004/24, 2004/27 and 2004/28.

*All these documents are available in Eudralex*

Detailed guidelines are given in Eudralex, Volume 9: “EU Pharmacovigilance Rules for Human and Veterinary Medicinal Products”. These guidelines are also applicable in Norway.

According to the requirements in Regulation 726/2004 and Directive 2001/83/EC, reports of adverse drug reactions involving authorised medicinal products for human use should be transmit-

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ted electronically as from November 2005. (See Circular 5/2005 from the Norwegian Medicines Agency).

The abovementioned legislation and especially the guidelines give a detailed description of the obligations of the Marketing Authorisation Holders (MAHs) and the national competent authorities to set up pharmacovigilance systems in order to exchange information about suspected adverse drug reactions. Consequently, detailed guidance is not included in this document. MAHs should refer to the latest version of the abovementioned documents. Nevertheless, the most important definitions are listed below (See Definitions).

### **Useful documents and web sites**

National regulation: "Forskrift om legemidler" <http://www.lovdata.no/cgi-wift/ldles?doc=/sf/sf/sf-19991222-1559.html>

EudraVigilance: <http://www.eudravigilance.org>

Eudralex: <http://pharmacos.eudra.org/F2/eudralex/index.htm>

## **NATIONAL REQUIREMENTS**

The Norwegian Medicines Agency (NoMA) has made one exception from the legislation referred to in this document. The NoMA would prefer not to receive Individual Case Safety Reports (ICSRs) regarding serious, unexpected adverse drug reactions originating from countries outside the EEA (=non-EEA-reports). According to the current requirements, these reports should be sent to the EMEA (EudraVigilance). As from 20<sup>th</sup> November 2005 all MAHs should send such reports electronically to EudraVigilance. The NoMA has access to non-EEA reports in the EudraVigilance database.

## **DEFINITIONS**

### **Adverse Reaction/ Adverse Drug Reaction (ADR):**

Adverse reaction means a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

### **Serious Adverse Reactions:**

Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital abnormally/birth defect.

### **Non-Serious Adverse Reactions**

An adverse reaction which does not meet the criteria of a serious adverse reaction.

### **Unexpected Adverse Drug Reaction:**

Unexpected Adverse Reaction means an adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristic.

**Spontaneous Reports:**

A communication to a company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicinal products and which does not derive from study.

**The Member States:**

The countries in EEA (including EU Member States)

**EMEA:**

European Medicines Agency

**EudraVigilance:** The European pharmacovigilance database localised at the EMEA.

**HANDLING OF ADVERSE DRUG REACTION REPORTS**

The Norwegian Medicines Agency (NoMA) receives adverse drug reaction reports from health care professionals in Norway via the regional pharmacovigilance centres (RELIS). In addition the NoMA receives reports of all serious adverse drug reactions occurring in Norway (as ICSRs) from MAHs. The NoMA is responsible for forwarding information regarding all serious adverse drug reactions occurring in Norway to the EMEA. Therefore, the MAHs should not send serious reports originating from Norway directly to the EMEA, as this will result in duplicates in the European database (EudraVigilance).

Serious adverse drug reactions occurring in other EU/EEA-countries should be reported to the competent authority in the Member State in whose territory the incident occurred. The MAHs are responsible for reporting adverse drug reactions occurring in countries outside the EEA to the EMEA.

Non-serious adverse drug reactions are collected by the MAHs and sent to the relevant competent authorities as Periodic Safety Update Reports (PSURs). The NoMA informs the MAHs of non-serious adverse drug reactions in the form of annual/semi-annual line-listings.

An overview of the handling of adverse drug reaction reports are given in the flow charts below.

**FOLLOW-UP INFORMATION AND PRIORITIES**

When RELIS/NoMA receives adverse drug reaction reports from health care professionals, all relevant information is registered in the national pharmacovigilance database. If essential information about the case is lacking, RELIS/NoMA would try to obtain additional information before the report is sent to the MAHs. If this information is not received by RELIS/NoMA within the timeframe of forwarding the report, details of the requested information will be stated in the report in order to reduce the MAHs need to request additional information. All relevant follow-up information which the NoMA receives will be automatically forwarded to the relevant MAHs.

However, the NoMA still receives a substantial number of follow-up information requests from the MAHs. The NoMA does not have the capacity to follow-up all cases of adverse drug reactions and follow-up requests will be prioritized according to the following order:

These are the criteria for case prioritization;

- 1) Serious and unexpected adverse reactions **or** drugs of special interest
- 2) Serious and expected adverse reactions **or** non-serious and unexpected adverse reactions.
- 3) Non serious and expected adverse reactions

Our internal guidelines for case prioritization are based on the guideline published by the CIOMS-V working group, “*Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V*”, 2001 (ISBN 92 9036 074 7). This document is available from the World Health Organisation (see: [www.cioms.ch](http://www.cioms.ch), e-mail: [cioms@who.int](mailto:cioms@who.int))

The CIOMS-V working group has developed a set of lists of information that should be available for each of the case categories described above. List A includes information that should be available in the reports of the lowest priority (non-serious and expected adverse reactions). List B contains the additional information that should be requested for reports of the second priority. List C contains further data elements which are considered important for the reports of the first priority. Lists A, B and C can be found in Appendix 7, page 293, in the guideline mentioned above.

The NoMA kindly asks the Norwegian affiliates of MAHs to thoroughly assess all questions received from central pharmacovigilance units/headquarters. Today, the NoMA receives a substantial number of requests/questions regarding information that is already adequately coded in the report originally sent to the MAHs.

## **ADVERSE DRUG REACTION REPORTS WHICH FALL UNDER DIFFERENT REGULATIONS**

In some cases an adverse drug reaction report could fall under both the regulations for spontaneous reports and the regulations for clinical trials.

As a principal rule:

- all adverse drug reactions from **interventional studies** should be reported to EudraVigilance – Clinical Trial Module (EV-CTM)
- all adverse drug reactions from **non-interventional studies** should be reported to EudraVigilance – Post-Authorisation module (EV-PM)
- no reports are to be sent to both ***EV-CTM and EV-PM***

The NoMA considers the guidelines in Volume 9 and in “Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reaction (EudraVigilance – Clinical Trial Module)”, which describes several specific situations, to be applicable in Norway.

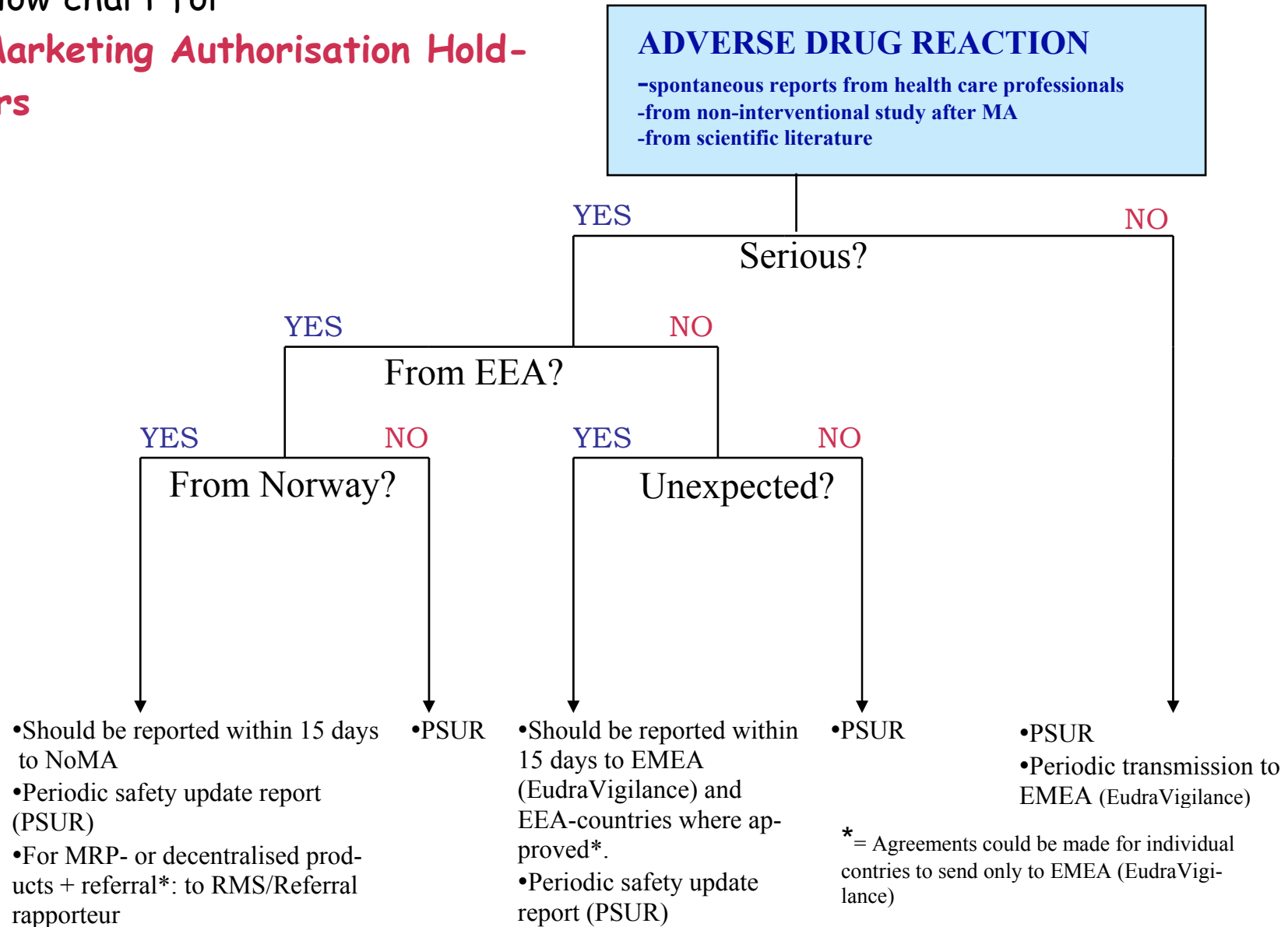
## **ADDITIONAL INFORMATION**

It is of great importance that the MAHs, in their adverse drug reaction reports, use the name (active substance name or trade name) of the medicinal product as it is stated by the reporting health care professional. In most Norwegian cases this means that the MAHs should use the approved Norwegian trade name of the medicinal product when reporting adverse drug reaction to the NoMA.

ICSRs which are based **only** on information received from the NoMA, should not be transmitted (back) by the MAHs to the NoMA. This rule applies even if the MAHs have made causality assessments differing from those of the NoMA.



## Flow chart for Marketing Authorisation Hold- ers





## Flow chart for The Norwegian Medicines Agency

