

Guidance for Industry on Providing Regulatory Information in Electronic Format in the Netherlands:

Electronic submission of expedited Individual Case Safety Reports (ICSRs)

Medicines Evaluation Board
Kalvermarkt 53
2511 CB The Hague
P.O.Box 16229
2500 BE The Hague
tel. +31 70 356 74 00
fax +31 70 356 75 15
Internet: www.cbg-meb.nl

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Change Record

Version	Author(s)	Comments
1.0 March 2005	Anja van Haren	
1.1 April 2006	Anja van Haren	- Clarification of testing requirements for EVWEB users. - Overview table (Annex 1) with testing scenarios added.
1.2 August 2006	Anja van Haren	- Updated Section 3 following upgrade of MEB local software (differences between EMEA application and local system) - Added section concerning receiving ICSRs by MAHs
1.3 January 2007	Anja van Haren	Updated section "Relevant Documents" with respect to ICH M2 recommendations
1.4 May 2009	Anja van Haren	Updated references from E2B(M) to E2B(R2) Updated references from Volume 9 to Volume 9A Updated sections 5 and 6

1. Introduction

This Guidance Document is intended to assist pharmaceutical companies in the submission of Individual Case Safety Reports (ICSRs) in electronic format to the Medicines Evaluation Board Agency (MEB Agency). All Marketing Authorisation Holders in the European Economic Area (EEA) are responsible for implementing standards that ensure electronic communication with regulatory authorities in full compliance with the standards agreed at the level of ICH¹ and Community guidelines as referred to in Article 106, paragraph 1 of Directive 2001/83/EC. In accordance with Community legislation (article 24 of Regulation No 726/2004 and article 106 of Directive 2001/83/EC as amended) reports of adverse drug reactions involving authorised medicinal products for human use should be transmitted electronically as from November 2005.

The revision of Volume 9A of the Rules Governing Medicinal Products in the European Union (Part III) reflects the requirements for mandatory electronic reporting of adverse reactions. It applies to national competent authorities, the EMEA and Marketing Authorisation Holders (MAHs) in the EEA. Therefore this document also informs MAHs about receiving ICSRs in electronic format from the Netherlands Pharmacovigilance Centre Lareb, which is done in collaboration with the MEB Agency.

The ICH guidelines describing the requirements for electronic transmission of ICSRs can be obtained from the ICH website² and are also given in Volume 9A of *The Rules Governing Medicinal Products in the European Community*³. Information regarding the required standards, formats and guidelines are also available on the EudraVigilance website (the European data-processing network and database management system for the exchange, processing and evaluation of Individual Case Safety Reports)⁴.

Electronic transmission of SUSARs (Suspected Unexpected Serious Adverse Reaction Reports) as defined in the Clinical Trial Directive (Directive 2001/20/EC of 4 April 2001) falls outside the scope of this document.

2. ICH Guidelines

It is expected that implementation of the ICH standards by all parties involved will improve the rapid exchange of information and the capability of regulators and pharmaceutical industry to use pharmacovigilance data in a standardised way. Three main aspects have to be considered: the ICH specifications for data-model and safety reports, secure Gateway communication and use of controlled vocabularies.

2.1 Reporting: ICH E2B(R2) & M2 Message and Case Safety Report Specification

The implementation of electronic data exchange and management requires the use of common data elements and the syntactical definition of the electronic message. The E2B(R2) (*previously coded E2B(M)*) document provides a detailed breakdown of the data elements for all types of ICSRs, as well as notes on transmission and user guidance information. The ICH M2 Expert Working Group elaborated the

¹ The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

² <http://www.ich.org>

³ <http://pharmacos.eudra.org/F2/eudralex/index.htm>

⁴ <https://eudravigilance.emea.europa.eu>

syntactical definition of the electronic message allowing safety messages, containing information for one or more ICSRs to be exchanged between one sender and one receiver in one transaction.

The sender of the ICSR will receive feedback that acknowledges receipt of the transmitted message as well as validating that each ICSR is syntactically correct and that data for all mandatory fields are provided. ICH M2 has developed a specification for such 'Acknowledgement Message'.

XML (eXtensible Markup Language) is the adopted standard for the exchange of Safety and Acknowledgement Messages in the European Economic Area. A valid XML Safety or Acknowledgement Message needs to include an XML header and a Document Type Definition (DTD) reference. In this context, the character set used for the Safety and Acknowledgement Messages must also be declared. The accepted character sets are for Safety Messages LATIN-1 (ISO-8859-1) and UNICODE (UTF-8; UTF-16). The Acknowledgement Messages are returned in UTF-16 for language compatibility. The complete reference documentation Electronic Transmission of Individual Case Safety Report Message Specification version 2.3 (ICH ICSR DTD Version 2.1) is available at the EudraVigilance website.

2.2 Communication: ICH M2 ESTR I Gateway

A Gateway is defined as a data exchange service, which consists of all core standards and functionalities required for supporting the standards of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (e.g. Simple Mail Transfer Protocol/Secure Multipurpose Internet Mail Extension - SMTP/SMIME- protocol). The EMEA (European Medicines Agency) has implemented an electronic regulatory submission environment, the EudraVigilance Gateway, which follows the ICH M2 Gateway Recommendation for the Electronic Safe Transfer of Regulatory Information (ESTRI-Gateway).

The EudraVigilance Gateway is providing a single point of contact between MAHs (Marketing Authorisation Holders) and applicants as well as Regulatory Authorities in the European Economic Area. By doing so, the EudraVigilance Gateway is considered a hub and all the connections for the MAH, applicants, sponsors and Regulatory Authorities are known as spokes. The EudraVigilance Gateway reads the sender and receiver information specified in the safety or acknowledgement messages and routes the message to the appropriate receiver. Only those parties that are registered with the EMEA are able to exchange safety messages either with the EMEA or other registered parties, including Regulatory Authorities. MAHs and applicants are responsible for implementing at least one of the multiple ESTR I standards in order to ensure electronic communication with any Regulatory Authority.

2.3 Controlled vocabularies: ICH Topic M1 and M5

Structuring of data, as required for electronic transmission, implies the use of controlled vocabularies.

2.3.1 MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA, the internationally agreed medical terminology, has been developed under the auspices of ICH (ICH topic M1). This new international medical terminology is particularly important in the electronic transmission of adverse event reporting, both in the pre- and post- marketing areas, as well as the coding of clinical trial data. In the European Economic Area use of MedDRA for all adverse drug reaction reporting became mandatory in January 2003. More information about MedDRA can be obtained from the following website: <http://www.meddramsso.com>.

2.3.2 Medicinal Product information

In November 2003 the ICH M5 Working Group has been established to develop a new tripartite guideline that defines the Data Elements and Standards for Drug Dictionaries supporting all aspects of pre- and post- approval pharmacovigilance activities as well as communication of regulatory information. The ICH M5 objectives are to build on what is currently available in the regions and to support the population of existing systems / applications with fully reliable regulatory medicinal product information and not to build and maintain a full-fledged drug dictionary.

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In the absence of a current agreement for specifying product information, the EMEA has developed the EudraVigilance Medicinal Product Dictionary (EVMPD). As such the EVMPD provides integrated standard terminology for active ingredients, excipients, pharmaceutical forms, routes of administrations, concentration ranges and units, country codes, MAH and sponsor data. Although it is not mandatory, MAHs and applicants are strongly encouraged to populate the EVMPD with their investigational medicinal products and authorised products. For more information about EVMPD and the data collection process, please visit the EudraVigilance website.

3. Implementation of E2B(R2) at the MEB Agency

In order to facilitate on the national level the technical implementation of the electronic transmission of ICSRs by Marketing Authorisation Holders, the MEB Agency has obtained a licence from the European Commission for use of the software developed for and in collaboration with the EMEA for the EudraVigilance project. The EudraVigilance application installed at the MEB Agency is fully compatible with the ICH E2B(R2) and M2 specifications. It allows to send, receive and process ICH conform safety messages automatically, to validate all incoming messages including integrity and consistency checking and to generate acknowledgements related to the outcome of the transaction.

The main difference between the EMEA system and MEB's system with possible impact for MAHs is the way messages with Clinical Trial reports are being handled. Similar to the EMEA system it is not possible to mix PM and CT reports in a single message. However, where the EMEA system uses separate Organisation Identifiers (EVHUMAN and EVCTMPROD) to decide which set of business rules will be applied, the MEB Agency uses just one Organisation Identifier (CBGMEB) for both the CT and the PM module. The first report in the message defines which set of business rules will be applied to the complete message:

- If the first report in a message is a CT SUSAR, the complete message will be validated against SUSAR business rules. If there are PM reports in this message, 02 ACKs will be generated for these PM reports.
- If the first report in a message is a PM case the complete message will be validated against PM business rules. If there is a CT report in this same message, a 02 ACK will be generated for these CT reports.

This is particularly important for MAHs sending more than one case report in a single message. As MAHs are already used to handle these two kinds of reports in separate messages for each EMEA identifier, it is expected that most MAHs do not have major problems with this approach.

The maximum field lengths as specified by ICH E2B(R2) have been implemented in the MEB local system. There is no other deviation from the EMEA business rules described in "Note for Guidance EudraVigilance Human Version 7.0 Processing of Safety Messages and Individual Case Safety Reports (ICSRs) 3 August 2004 Doc. Ref. EMEA/H/20665/04/Final".

3.1 Testing electronic submission of ICSRs with the MEB Agency

Since the software application at the MEB Agency is basically similar to the application at the EMEA difficulties regarding validation of ICSRs and/or E2B(R2) interpretation differences are not expected if you have already successfully completed the EMEA testing programme. However, technical issues can not be excluded to occur and a test phase needs to be successfully performed before electronic transmission of ICSRs can replace sending paper reports.

Once your organisation has successfully completed the EMEA testing programme, you can contact the

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Dutch EudraVigilance Coordinator Anja van Haren (a.v.haren@cbg-meb.nl, telephone + 31 (0) 70 356 74 96) in order to make an appointment regarding the initial testing. Please provide answers to the following questions:

- Who is the contact person for E2B submissions within your organisation?
- What is your profile id (test and production environment) on the EMEA Gateway?

For the initial test the MEB Agency would like to receive testfiles similar to those used previously in testing with the EMEA. Organisations should provide the following 9 sample cases, which should contain realistic data but do not need to be real cases:

1. Fatal report with cause of death and autopsy sections filled in
2. A follow up report (sent in after the initial report)
3. A report including patient medical and drug history
4. A parent child report
5. A nullification report
6. A report where the worldwide unique safety report number (A.1.10) is either a Regulatory authority's case report number (A.1.10.1) or a Other sender's case report number (A.1.10.2) that is different from the sender's safety report unique identifier (A.1.0.1)
7. A non-intervention study (observational) report
8. A case reported in the literature
9. A report with the section report duplicate (A.1.11.1) completed

The initial test cases should be sent to the test-database by using the following identifier: CBGMEB1 (the production-identifier is CBGMEB). The CIOMS forms are preferably send by e-mail to Anja van Haren (a.v.haren@cbg-meb.nl). If the CIOMS forms are sent by fax/paper, clearly indicate that these CIOMS forms are submitted for E2B **testing** purposes. Please also attach the table in Annex 1 of this Guidance document to clarify which case-number relates to a specific scenario. This table will be used for giving feedback on each specific test case.

Upon successful completion of the test phase your company will be ready to start electronic transmission of ICSRs to the MEB Agency. The currently established regulatory reporting mechanism (paper reporting or e-mail reporting of CIOMS-forms) will be further maintained for 3 months (or a minimum of 20 safety messages) whereby the MEB Agency may decide to shorten or extend it. This will allow comparison of the submitted data and ensure quality assurance and data consistency. The paper reporting will represent the legal regulatory reporting mechanism until agreement on fully electronic transmission is achieved. A date for changing reporting method will be agreed between both parties and the MEB Agency will confirm this in writing.

4. Technical failure

For instructions on how to act in case of communication failure you are referred to the EMEA's "Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre-and Post-authorisation Phase in the European Economic Area (EEA) (Document dated 29 October 2004, Doc. Ref: EMEA/115735/2004)". This document also describes the implications of electronic reporting with regard to the legal reporting compliance as defined in Community legislation and the evaluation steps. The MEB Agency fully underwrites the procedures that have been agreed in this document and expects that all parties will adhere to these procedures in case of communication failure.

If you are under pressure to meet reporting requirements you are advised to follow the following procedure, in line with above mentioned Guidance document:

Revert to previously established methods, like sending CIOMS forms via e-mail, fax or post (paper, cd-

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rom). The paper report(s) transmitted should be clearly marked with 'FAILURE OF ELECTRONIC SAFETY MESSAGE GENERATION AT SENDERS SIDE'. The MAHs date of sending the CIOMS forms will be sufficient to prove regulatory compliance in an inspection. You are requested to send the reports electronically in E2B via the Gateway once your system is operational again. In order to avoid duplicates the paper report will not be processed in the MEB database, but only stored for compliance purposes.

The e-mail address for sending electronic CIOMS forms is: adr15d@cbg-meb.nl.

The address for sending paper reports (or electronic reports on physical media):
Medicines Evaluation Board
attn. EudraVigilance Coordinator
PO Box 16229
2500 BE The Hague
The Netherlands

5. Small and Medium Size Enterprises using EVWEB

To support small and medium size organisations not having the financial resources available to put the technical infrastructure for electronic adverse drug reporting in place, the EMEA has developed EVWEB, a web based application, that will allow organisations to report electronically in the agreed ICH standards. Such companies can make use of MedDRA at a reduced rate (depending on the number of reports per year and company turnover) for the submission of ICSRs and they are therefore strongly advised to investigate the possibilities of this EVWEB. Access to EVWEB will be granted following completion of a training programme, to make sure that you are familiar with the concepts of electronic reporting requirements and the web application.

Organisations using EVWEB for data entry do not need to complete the testing procedure with the MEB as described in section 3. However, if E2B(R2) files are created from a local database and the EVWEB system is only used for sending the files ('post function') it is required to follow the testing procedure.

Organisations that have successfully completed the EudraVigilance Training Course and wish to use EVWEB for submitting reports to the MEB Agency should contact the Dutch EudraVigilance Coördinator Anja van Haren (a.v.haren@cbg-meb.nl, telephone + 31 (0) 70 356 74 96) before first transmission. Please indicate whether you will use EVWEB for both data entry and sending ICSRs or for sending ICSRs only ('post function'). Furthermore, please provide your organisation identifiers (test if applicable, but at least for the production environment). This will allow the MEB to make the necessary technical preparations for receiving cases from your organisation. If you fail to notify the MEB in advance, the ICSRs will be rejected by the system and no Acknowledgement Message will be returned.

More information about EVWEB and the training programme can be found on the EudraVigilance website.

6. Receiving Dutch Authority ICSRs

By European law each Member State should have in place a system for the collection of spontaneous suspected adverse reaction reports from healthcare professionals, MAHs and where appropriate from patients/consumers. In the Netherlands the spontaneous reporting system is maintained by the Netherlands Pharmacovigilance Centre Lareb (previously known as the Netherlands Pharmacovigilance Foundation).

As from September 2006 MAHs can receive Lareb reports in accordance with ICH E2B(R2) guidelines via

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the Gateway or via e-mail:

1. The ICSRs will be extracted from the Lareb database. Please note the following:

- Files are created in accordance with EMEA EV7 business rules.
- The narrative is written in Dutch and contains a brief English summary;
- Field B.2.i.0 <primarysourcereaction> contains Dutch language;
- The language code is 'NL': <ichicsr lang="nl">

2. These messages can be sent to MAHs via the MEB Cyclone Gateway connection, using the MEB identifiers (CBGMEB for the production environment).

The MAH is responsible for processing case reports in their local system appropriately. The MEB Agency and Lareb do not intend to check this procedure. It is important that the Worldwide Case ID remains the same throughout re-transmissions of ICSRs. The MAH is strongly advised to check whether the field <authoritynumb> is handled in line with ICH E2B(M) recommendations.

On request of MAHs Lareb does not only send serious cases, but also non-serious cases. It is not possible to receive only non-serious cases or only serious cases. However, the serious cases will be separated from the non-serious cases in different messages.

Lareb does not process Acknowledgement messages returned by MAHs. Since all ICSRs are also sent to the EMEA, only the Acknowledgment returned by the EMEA will be checked by Lareb. If the EMEA returns a negative Acknowledgement, the case involved will be corrected and sent again.

Organisations that wish to receive expedited Lareb reports in accordance with ICH E2B(R2) guidelines via the Gateway or via e-mail should contact the Netherlands Pharmacovigilance Centre Lareb at info@lareb.nl. Please provide the following information:

- Organisation name and address
- Contactperson (name, function, e-mail address and telephone number)
- Your organisation identifier for the production environment if you wish to receive via the gateway.

7. Closing remarks

Any comments on or queries concerning this guidance can be addressed to:

Anja van Haren
Medicines Evaluation Board
PO Box 16229
2500 BE The Hague
The Netherlands
tel +31(70)3567496
fax +31(70)3567515
e-mail: a.v.haren@cbg-meb.nl

Frequently Asked Questions related to E2B(R2) submissions will be published on the MEB website and updated as necessary.

Relevant Documents

- ICH E2B(R2) – Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for transmission of Individual Case Safety Reports: Version 4.4.1 – 5 February 2001
- E2B Q&As (R5) Implementation Working Group questions and answers version dated 3 March 2005
- ICH M2 – Electronic Transmission of ICSRs Message Specification: DTD version 2.1: Version 2.3 Document Revision February 1, 2001
- ICH M2 Gateway Recommendation for the Electronic Transfer of Regulatory Information (ESTRI Gateway, see <http://estri.ich.org>)
- Technical Documentation – Note for Guidance EudraVigilance Human Version 7.0 Processing of Safety Messages and individual Case Safety Reports (ICSRs) (Document dated 3 August 2004, Doc. Ref. EMEA/H/20665/04/Final).
- Note for Guidance on the electronic data interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in pharmacovigilance during the pre- and post-authorisation in the European Economic Area (EEA). (Document dated 29 October 2004, Doc. Ref: EMEA/115735/2004)

Annex: Overview table testscenario's

Test Number	Test description	Safety Report ID	MEBComments
1	Fatal report with cause of death and autopsy sections filled in		
2	A follow up report		
3	A report with a patient who has previous medical and drug history		
4	A parent child report		
5	A nullification report		
6	A report where the worldwide unique safety report number (A.1.10) is a Regulatory authority's case report number (A.1.10.1) including the sender's own unique safety report ID (A.1.0.1)		
7	A non-interventional study report		
8	A literature report		
9	A report with section report duplicate (A.1.11.1) completed		

General comments

- 1.
- 2.