European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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IMPLEMENTATION PLAN FOR THE NOTE FOR GUIDANCE EUDRAVIGILANCE HUMAN – PROCESSING OF SAFETY MESSAGES AND INDIVIDUAL CASE SAFETY REPORTS (ICSRS)

(Doc. Ref. EMEA/H/20665/04/Final, Revision 1)

1 Background

The Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1) describes the new aspects of Safety Message processing, ICSR validation and acknowledgment generation in the European Economic Area (EEA). It was prepared by the EudraVigilance Expert Working Group (EV-EWG) in response to the EudraVigilance Action Plan (Doc. Ref. EMEA/82645/2007), which was adopted by the Heads of Medicines Agencies (HMA-Human) in Bonn, Germany in April 2007 and endorsed by the EMEA Management Board in London, UK in June 2007.

It updates and replaces the business rules and validation steps as described in the 'Note for Guidance – *EudraVigilance Human Version 7.0* – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)' (Doc. Ref. EMEA/H/20665/04/Final).

The note for guidance represents a consensus view and is applicable to all stakeholders, which are exchanging Safety/Acknowledgement Messages and ICSRs electronically in the EEA in line with Community legislation (Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A of The Rules Governing Medicinal Products in the European Union Part III: Guidelines for Marketing Authorisation Holders, Competent Authorities and the Agency on Electronic Exchange of Pharmacovigilance Information in the EU and Volume 10, Clinical Trials Guidelines Chapter II: Monitoring and Pharmacovigilance).

2 Scope of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1)

The scope of the revised Note for Guidance is to improve the quality and consistency of ICSRs reported electronically to EudraVigilance. This has been achieved by strengthening of the validation process of ICSR ICH E2B(R2) data elements and by making mandatory the population of certain ICH E2B(R2) data elements.

The improvement of the data quality is of major importance as regards the following aspects:

- Supporting the EU pharmacovigilance and risk management activities mainly in the area of signal detection, case assessment and the evaluation of potential safety issues,

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- Monitoring the safety of patients enrolled in clinical trials and allowing for the adequate association of reported suspected unexpected serious adverse reactions (SUSARs) with the relevant study, the investigational medicinal product(s) (IMPs) or a specific country,
- Preparing for the implementation of the EudraVigilance Access Policy.

A summary of the revised validation rules and the new mandatory E2B(R2) ICSR data elements is provided in Annex 1.

3 Objective of the Implementation Plan

The objective of this Implementation Plan is to outline a coordinated implementation approach of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1) in the EEA. Since a large number of stakeholders in the Community now apply the electronic transmission of ICSRs, any changes of the validation procedures require a common approach to avoid disruptions in the data exchange. Therefore, all stakeholders are required to apply the implementation approach as outlined in Chapter 4.

4 Implementation Approach

The implementation of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1) should be approached by all stakeholders based on the following two aspects:

4.1 Data Entry and Data Management

The revised business rules represent a best practice guide related to the preparation and electronic exchange of ICSRs. All stakeholders are required to apply the new business rules in preparing and processing ICSRs no later than **01 January 2010**.

This approach does not require any immediate technical changes to the pharmacovigilance systems in use by stakeholders but refer in a first instance to the data entry and management practices of each stakeholder, which require alignment with the revised business rules.

4.2 Technical Adaptations of Pharmacovigilance Systems

Technical changes based on the revised business rules require a coordinated approach in the EEA to avoid major disruptions in the electronic exchange of ICSRs. The ICH E2B(R2) guideline[1] is currently under revision at the level of ICH. The technical implementation of the revised business rules is therefore scheduled at a later stage and will, where possible be coordinated with the implementation of the revised ICH E2B(R2) guideline.

The current validation process as described in the Note for Guidance – *EudraVigilance Human Version 7.0* – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)' (Doc. Ref. EMEA/H/20665/04/Final) remains unchanged. ICSRs, which do not comply with the new validations process and mandatory data elements detailed in the Note for Guidance EudraVigilance Human – Processing of Safety Messages and

[1] ICH ICH Harmonised Tripartite Guideline - Maintenance of the ICH Guideline On Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports E2B(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 5 February 2001

Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1) will currently not be classified as 'Error Reports' or 'Reports with Warnings' in the respective Acknowledgement Messages.

However, from **01 January 2010**, the EMEA will perform a routine data quality control based on the updated business rules and validation steps. Senders will receive on monthly basis listings of ICSRs, which do not comply with the mandatory data elements and validation rules as described in the revised Note for Guidance (see also Annex 1).

A corrected version of affected ICSRs, classified as 'Error Reports' according to the revised guidance, should be retransmitted electronically by the Sender to the appropriate EudraVigilance module immediately and no later than 15 days.

For ICSRs originating in the EEA and reported initially by Marketing Authorisation Holders (MAHs)/Sponsors of clinical trials to one or more National Competent Authorities (NCAs), the MAHs/Sponsors will be also required to send a corrected version of the affected ICSRs, classified as 'Error Reports' according to the revised guidance, to the concerned NCAs (see also Annex 1). The NCA of the primary source country/occurrence country will be required to forward the corrected reports to the appropriate EudraVigilance module based on the current reporting rules as set out in Community legislation and which are further detailed in Volume 9A and Volume 10. This process should also take place immediately and no later than 15 days by MAHs/Sponsors and the NCA concerned.

5 Training

Training as regards the requirements outlined in the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1) will be provided in the frame of the EudraVigilance training programme and the EudraVigilance Information Days.

Annex 1 Summary of mandatory ICH E2B(R2) data elements and new validation rules

New mandatory ICH E2B(R2) data elements		
Validation outcome	**Description**	**Objectives**
Classified as error in case of non compliance	• Identification of the country of the primary source *(ICH E2B(R2) A.1.1)*	• Systematic identification of the primary source country in the ICSRs
	• Primary source qualification *(ICH E2B(R2) A.2.1.4)*	• Identification of healthcare professional reports from non-healthcare professional reports
	• Seriousness *(ICH E2B(R2) A.1.5.1)*	• Differentiation of serious reports from non-serious reports
	• Seriousness criteria (for serious reports) *(ICH E2B(R2) A.1.5.2)*	• Identification of the seriousness criteria in ICSRs
	• Outcome of reaction/event at the time of the last observation *(ICH E2B(R2) B.2.i.8)*	• Identification of fatal reactions • Provide information on outcome for each reaction • Data quality control
	• Characterisation of drug role *(ICH E2B(R2)B.4.k.1)*	• Systematic identification of the drug role (*Suspect, Concomitant, Interacting*)
	• Active substance name (for reports submitted to EudraVigilance Clinical Trial Module when the drug is considered suspect or interacting) *(ICH E2B(R2) B.4.k.2.2)*	• Identification of the suspected or interacting active substances in reports originating in interventional clinical trials
Classified as warning in case of non compliance	• Active substance name (for reports submitted to EudraVigilance Post-Authorisation Module when the drug is considered suspect or interacting) *(ICH E2B(R2) B.4.k.2.2)*	• Identification of the suspected or interacting active substances in spontaneous reports or reports from non-interventional studies

New Validation rules		
Validation outcome	**Description**	**Objectives**
Classified as error in case of non compliance	• All reported country names, including the first part of the 'Worldwide unique case identification number', should be valid ISO3166 country codes	• Standardisation of reported data • Consistency check with primary source country
	• For spontaneous reports and reports originating from non-interventional studies, at least one reaction should have a fatal outcome if the ICSR is serious and with a seriousness criteria 'Results in death'	• Consistency check between the report seriousness criteria and reaction outcome • Identification of fatal reactions
	• Seriousness criteria should match with the ICSR seriousness	• Consistency check between the seriousness of the report and the seriousness criteria of the report
	• At least one drug in the report should be 'suspect' or 'interacting'	• Identification of suspected or interacting drug(s)
	• No follow-up report can be submitted for cases which have been previously nullified. An error message will be generated for any additional follow-up report submitted for this case	• To avoid re-use of the worldwide unique case identification number once it has been nullified
	• For any transmission to the EudraVigilance Clinical Trial Module, - The 'Study name' data element should contain: a) For SUSARs originating in the EEA: - 'Valid EudraCT Number#Study abbreviated name', b) For SUSARs originating outside the EEA: - 'Valid EudraCT Number#Study name' or - '#Study abbreviated name'	• Identification of the interventional clinical trial in which the SUSAR(s) originated for interventional clinical trials authorised in the EEA • Identification of the suspected or interacting active substances in the reports originating in interventional clinical trial

New Validation rules		
Validation outcome	**Description**	**Objectives**
Classified as error in case of non compliance	• Any report from study transmitted to the EudraVigilance Post-Authorisation Module, should have the data element 'Study type' populated with 'individual patient use' or 'other studies'	• Differentiation of spontaneous reports from reports originating in non-interventional study
	• The 'Test Name' data element (ICH E2B(R2) B.3.1c) should be populated with a valid lower level term (LLT) MedDRA term or code	• Standardisation of reported test name
	• Only numeric LLTs MedDRA codes should be used in designated fields (except in the data element 'Test Name' where valid LLTs MedDRA terms are also accepted)	• Standardisation of reported data
	• Values of age, weight and height should not be above 150 years, 650 Kg and 250 cm respectively	• Data quality control
	• All dates except the message date and the transmission date of the ISCR should be inferior or equal to the date of receipt of the most recent information	• Data quality control
	• All start dates should be inferior or equal to their corresponding end dates	• Data quality control
	• All dates (including imprecise dates) should not be in the future	• Data quality control
Classified as warning in case of non compliance	If the data element 'Pharmaceutical form (Dosage form)' is populated, the value should match with the latest version of the European Pharmacopoeia Pharmaceutical Forms list (See http://eudravigilance.emea.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp)	• Standardisation of reported data