EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 April 2015
EMA/762563/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Good practice guide on recording, coding, reporting and assessment of medication errors

Draft

Draft finalised by Project and Maintenance Group 1 of Member States and EMA pharmacovigilance governance structure	5 December 2014
Draft consulted with the European Commission's Patient Safety Quality of Care Working Group (PSQCWG)	11 February 2015
Draft agreed by Pharmacovigilance Risk Assessment Committee (PRAC)	12 February 2015
Draft agreed by the Implementation Group (IG) of Member States and EMA pharmacovigilance governance structure	18 February 2015
Draft circulated to the Committee for Human Medicinal Products (CHMP) and the Co-ordination group for Mutual recognition and Decentralised procedures – human(CMD-h)	19 February 2015
Draft agreed for public consultation by the European Risk Management Strategy Facilitation Group (ERMS-FG)	17 March 2015
Draft released for public consultation	14 April 2015

Comments should be provided using this template. The completed comments form should be sent to medicationerrors2013@ema.europa.eu by 14 June 2015.

Keywords	*Medication errors, pharmacovigilance, good practice, ICSR reporting, intercepted error, potential error, adverse reaction, MedDRA coding, PSUR, RMP, patient safety;*

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

As part of the public consultation of the good practice guide on recording, coding, reporting and assessment of medication errors the European Medicines Agency (EMA) would also like to take the opportunity to obtain stakeholder feed-back on the following questions:

1. With regard to recording medication errors in ICSRs, please provide comments on the proposal in Annex 4 for a business process for using the ICH E2B (R3) ICSR data element 'Additional Information on Drug' (G.k.10.r) and the data elements 'Sender's diagnosis' and 'Sender's comments'.

2. With regard to reporting medication errors in ICSRs do you consider the proposed disclaimer in chapter 5.7.2 useful to address potential conflicts between marketing authorisation holders' pharmacovigilance obligations and potential exposure to liability when classifying medication errors in suspected adverse reaction reports to national competent authorities or the Agency?

3. With regard to signal detection activities would you consider the development of methodological guidance on the detection of signals of medication errors in EudraVigilance useful, taking into account the Standard MedDRA Query (SMQ) for medication errors currently under development?

4. With regard to pharmacovigilance activities would stakeholders consider making available collated medication error reports via the EudraVigilance Data Analysis System (EVDAS) and/or the public adrreports.eu website in line with the revised EudraVigilance Access Policy useful? Please note that for the general public such reports would be presented by EEA and non-EEA geographic origin and based on a filter using coded MedDRA terms in combination with the data element 'Additional Information on Drug' (G.k.10.r) once the ICH E2B (R3) standard is implemented.

Good practice guide on recording, coding, reporting and assessment of medication errors

Table of contents

Executive summary

The European Union (EU) pharmacovigilance legislation has introduced a number of changes related to medication errors which affect the operation of pharmacovigilance systems in EU Member States. To support implementation of the new legal provisions amongst the stakeholders involved in the reporting, evaluation and prevention of medication errors the European Medicines Agency (EMA) in collaboration with the EU regulatory network was mandated to develop specific guidance for medication errors, taking into account the recommendations of a stakeholder workshop held in London in 2013.

This good practice guide is one of the key deliverables of the Agency's medication error initiative to clarify specific aspects related to recording, coding, reporting and assessment of medication errors in the context of EU pharmacovigilance activities with the objective to improve reporting and learning from medication errors for the benefit of public health.

1. Introduction (background)

Errors associated with the use of medicinal products are a major public-health burden. Medication errors generally refer to unintended mistakes in the processes of prescribing, dispensing or administering of medicinal products in clinical practice. An estimated 18.7 - 56% of all adverse drug events among hospitalised patients result from medication errors that would be preventable and are thus a concern at all stages of health care delivery in European health care systems[1].

2. Scope

The scope of this good practice guide includes the recording, coding, reporting and assessment of medication errors associated with suspected adverse reaction(s) in the context of EU pharmacovigilance obligations applicable to competent authorities in EU Member States, marketing authorisation holders and the Agency.

The primary purpose is to support competent authorities in EU Member States, marketing authorisation holders and the Agency to comply with their pharmacovigilance obligations detailed in Title IX of Directive 2001/83/EC and Regulation (EC) 726/2004, Chapter 3, Article 28 with regard to the recording, reporting and assessment of suspected adverse reactions (serious and non-serious) associated with an error in the prescribing, dispensing, preparation or administration of a medicinal product for human use authorised in the EU.

The recording, reporting and assessment of events associated with intentional overdose, abuse, misuse, occupational exposure and off-label use of medicines is outside the scope of this guidance.

EU good pharmacovigilance practices (GVP) require marketing authorisation holders to summarise information on medication errors regardless of whether they are associated with adverse reaction(s) in periodic safety update reports (PSUR) and to reflect the current knowledge about the risk of medication errors in risk management plans (RMP) for the purpose of continuous benefit-risk evaluation of medicinal products. This guide therefore also provides recommendations for marketing authorisation holders on the recording, coding, reporting and assessment of medication errors brought to their attention and which are not associated with adverse reaction(s).

[1] von Laue NC, Schwappach DL, Koeck CM. The epidemiology of preventable adverse drug events: a review of the literature. Wien Klin Wochenschr 2003; 115:407–415.

The scope of this guide also includes the Medical Dictionary for Regulatory Activities (MedDRA) coding conventions for medication error reports. Specific coding examples complementary to the guidance provided in the MedDRA Term Selection Points to Consider (MTS:PTC) document are provided.

The guidance acknowledges the fundamental role of patient safety reporting systems established in several EU Member States is to enhance patient safety by learning from potential failures of the healthcare system, including from medication errors which do not result in adverse reaction(s). However, authorities, bodies, organisations and/or institutions responsible for patient safety within EU Member States are outside the remits of Directive 2001/83/EC and Regulation (EC) No 726/2004 and medication errors not associated with adverse reaction(s) are not required to be reported as individual case safety reports (ICSR) in line with EU pharmacovigilance obligations.

In line with the provisions of Article 107a (5) of Directive 2001/83/EC one of the objectives of this guidance is the establishment of good practice for sharing information on medication errors associated with adverse reaction(s) between national competent authorities responsible for pharmacovigilance of medicinal products and authorities, bodies, organisations and/or institutions responsible for patient safety reporting and learning systems in EU Member States. A model of collaboration and exchange of information is introduced as an example for good practice acknowledging that EU Member States may use different models that best fit their national requirements for the exchange of information on medication errors.

3. Legal basis

Article 1(11) of Directive 2001/83/EC provides the definition of an adverse reaction (see chapter 4.2.) which covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including misuse and abuse of a medicinal product.

Recital (17) of Directive 2010/84/EC provides that Member States should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, including information on suspected adverse reactions arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure.

Accordingly, Article 101(1) of Directive 2001/83/EC lays down EU Member States' requirements to operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in humans, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

Article 107a (5) of Directive 2001/83/EC further requires EU Member States to ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that EU Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that EU Member State. From a public health perspective, it is good practice that competent authorities in EU Member States are also aware of adverse reactions associated with medication errors which may have been reported to a national patient safety organisation (PSO) or any other authorities, bodies, organisations and/or institutions responsible for patient safety within that EU

Member State. The provisions of Article 107a (5) of Directive 2001/83/EC recognise the broader remit of PSOs to tackle medication errors by introducing appropriate changes to clinical practice which is outside the legal remit of competent authorities in EU Member States.

Article 107a(5) of the Directive further requires that suspected adverse reaction reports arising from an error shall be appropriately identified in the standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients referred to in Article 25 of Regulation (EC) No 726/2004.

Each marketing authorisation holder is responsible for submitting PSURs for its own products according to Article 107b of Directive 2001/83/EC and Article 28 (2) of Regulation (EC) 726/2004. The legal basis for the submission of RMPs is provided in Article 8(3) (iaa) of Directive 2001/83/EC requiring that the application for a marketing authorisation shall be accompanied by a summary of the applicant's pharmacovigilance system and a risk management plan which describes the risk management system for the concerned product. The format and content requirements for PSUR and RMP are described in Articles 30 to 35 of the European Commission Implementing Regulation (EU) No 520/2012.

With regard to medication errors occurring in the context of clinical trials, Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, which will repeal Directive 2001/20/EC, lays down the reporting requirements for adverse events and serious adverse events by the investigator to the sponsor (Article 41) and the reporting requirements for suspected unexpected serious adverse reactions by the sponsor to EudraVigilance (Article 42). In addition, Annex III of Regulation (EU) No 536/2014 on safety reporting clearly states that medication errors, pregnancies and use outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

4. Definitions

The definitions provided in Article 1 of Directive 2001/83/EC should be applied for the purpose of this guidance; of particular relevance for ICSR recording, reporting and assessment activities are the definitions provided in GVP module VI together with this chapter which include general principles presented in the ICH E2A and E2D guidelines[2] and WHO guidance[3]. Also the definitions provided in the complementary guidance in chapter 4.5. should be adhered to.

4.1. Adverse event

Article 2 (32) of Regulation (EC) 536/2014 on clinical trials on medicinal products for human use, which will repeal Directive 2001/20/EC, defines an adverse event (AE) as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

A similar definition is provided in Annex I (Rev 3) of the GVP guideline: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. For the purpose of this

[2] http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
[3] WHO draft guidelines for adverse event reporting and learning systems (2005) (http://www.who.int/patientsafety/events/05/Reporting_Guidelines.pdf)

guidance medication related adverse events should be distinguished from other adverse events (e.g. fall, surgery on wrong body site etc.).

WHO defines an adverse event as an injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse events may be preventable or non-preventable.

4.2. Adverse reaction

An adverse reaction (ADR) is a response to a medicinal product which is noxious and unintended (Directive 2001/83/EC, Article 1(11)). This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorisation;
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.

This definition is provided in GVP Module VI.A.2.1 'Management and reporting of adverse reactions to medicinal products'.

4.3. Medication error

For the purpose of ICSR reporting in the EU, GVP Module VI.B.6.3 defines a medication error as any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer. This definition is focused on the management and reporting of adverse reactions to medicinal products and does not cover all stages of the medication use process where an error may occur and where there is an adverse reaction, e.g. preparation for administration.

For the purpose of this guidance and building on the GVP VI principles the following **conceptual definition** of a medication error is provided to allow for a common approach to recording, coding, reporting and assessment of errors in the drug treatment process regardless of whether the error is associated with adverse reaction(s):

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

The concepts of intentional overdose, off-label use, misuse and abuse as defined in GVP Module VI.A.2.1.2 are outside the scope of this guidance and should be clearly distinguished from medication errors.

For EU specific regulatory processes and pharmacovigilance reporting requirements for medication errors associated with ADRs please refer to chapter 5.3.

4.3.1. Medication errors and correlation with harm and preventability

Figure 1 below outlines the correlation of medication errors with harm and preventability from a patient safety perspective. An adverse reaction as a consequence of an error in the medication use process is considered preventable, in contrast to a non-preventable adverse reaction which may be labelled e.g. in SmPC section 4.8 as an undesirable effect of a medicine, i.e. the probability of harm to the patient is known and accepted and will likely occur depending on the frequency of the adverse reaction. There are also medication errors which do not necessarily result in harm (no ADR) but which

may have other unwanted effects e.g. from an economic or environmental point of view (e.g. drug prescribed and dispensed but not taken). If an error occurred but was identified and intercepted before reaching the patient, a potential adverse drug reaction was prevented and this is referred to as 'intercepted error'.

For learning purposes "potential errors" may also be relevant, e.g. if there are circumstances or information capable of leading to an error which are considered worthwhile to be recorded.

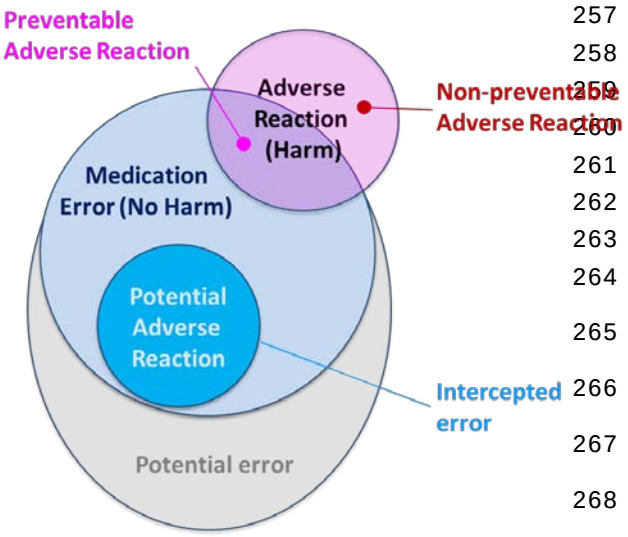


Figure 1: Correlation between medication errors, preventable and non-preventable adverse reactions and intercepted errors (modified according to Morimoto et al., Qual Saf Health Care 2004; 13:306-314). This figure is intended for illustrative purposes only to explain the concept of medication errors from a *patient safety* perspective without implications for pharmacovigilance reporting requirements.

4.3.2. Classification of medication error reports

For the purpose of this guide, the objective of which is to support the implementation of the EU pharmacovigilance requirements outlined in chapter 3. adverse reactions arising from medication errors (i.e. resulting in harm to the patient) should be recorded, reported and assessed.

Medication errors brought to the attention of MAHs but not resulting in harm, i.e. not associated with adverse drug reaction(s), may be relevant for the scientific evaluation and interpretation of safety data and of the benefit-risk profile of a medicinal product and should therefore be recorded and assessed in line with the recommendations of GVP Module VI.B.6.3, and GVP Module VII.B.5.9 and V.B.8.6.4 on periodic safety update reports and risk management planning respectively (see chapter 5.4.).

To facilitate this process it is important to adequately classify medication errors. Depending on where the break occurs in the chain of events leading to the error and its consequences for the patient, a clear distinction should be made between medication errors associated with adverse reaction(s), medication errors without harm, intercepted medication errors and potential medication errors as shown in figure 2. The definitions for intercepted and potential medication errors are provided in chapter 4.3.3. and 4.3.4. respectively.

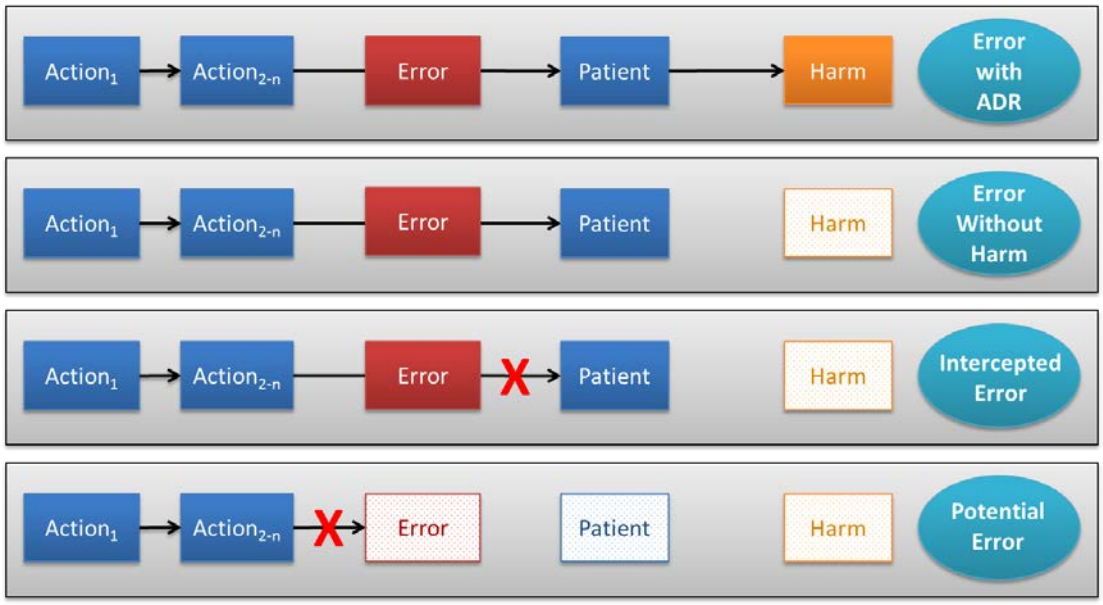


Figure 2: Concept for the classification of medication error reports for pharmacovigilance purposes. Depending on the break in the chain of events (represented by X), medication errors may be classified as error with ADR, error without harm, intercepted error and potential error.

4.3.3. Intercepted medication error ('near miss')

In the context of pharmacovigilance an intercepted error indicates that an intervention caused a break in the chain of events that would have resulted in a 'potential ADR' and the intervention has prevented actual harm being caused to the patient, e.g. a wrongly dispensed medicine was actually not taken by the patient because the error was noticed.

In the context of patient safety reporting systems the term 'near miss' is used for describing what is termed 'intercepted error' for pharmacovigilance purposes. A near miss from a patient safety perspective is a random break in the chain of events leading up to a potential adverse event which has prevented injury, damage, illness or harm, but the potential was nonetheless very near.

4.3.4. Potential medication error

According to GVP Module VII.B.5.9 a potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient.

The term potential medication error refers to an error which has the potency for various mistakes and may become reality at any time or it has already occurred. This includes all possible mistakes in the prescribing, dispensing, administration or preparation of a medicinal product by all persons who are involved in the medication process.

The potential error could lead or has led to

a) a medication error with harm, but without the awareness of the actual cause,

b) a medication error without harm, but without the awareness of the actual cause, or

c) a medication error without harm, but with the awareness of the actual cause and the subsequent prevention (intercepted error, see chapter 4.3.3.).

Following this approach the various mistakes could be clearly assigned to one or two of these categories (a, b or c). For example, the indication of the strength of the active substance of oral

solutions (drops) may vary between different marketing authorisation holders. Sometimes the strength on the label of oral solutions refers to 'mg/ml' sometimes to 'mg/dose'. Therefore it is necessary - before change of medication – to calculate these dose regimes to ensure that the dose applied remains unchanged. Otherwise, a patient could be exposed to an accidental overdose due to a misinterpretation with regard to the concentration and the real amount of active substance per dose. In accordance with the classification proposed this might have led to a medication error with or without harm in accordance with categories a) or b). If a pharmacist notices a false calculation before delivering the drug to the patient this case would fall under category c). The borders between these categories are fluent as described. In another example a pharmacist noticed that the names of two medicines are similar and could clearly lead to drug name confusion in practise, but there was no involvement of a patient actually taking the drug. This potential medication error could be assigned to above category c). Since no patient was involved consequently no harm could occur, but the potential for error exists and such potential cases of medication error should be included in the relevant PSUR sections to allow regulators to take action to minimise the risk of drug name confusion. In this example the MAH is encouraged to also inform the Agency's Name Review Group (see chapter 5.3.1.) if the medicine is authorised through the centralised procedure.

4.4. Root cause analysis

WHO International Classification for Patient Safety (ICPS) defines root cause analysis as a reactive form of risk assessment to inform the development of actions taken to reduce risk, as a systematic iterative process whereby the factors that contribute to an incident (error) are identified by reconstructing the sequence of events and repeatedly asking "why" until the underlying root causes (contributing factors or hazards) have been elucidated.

For the purpose of conducting root cause analysis where appropriate chapter 5.5.1. describes important parameters which may have contributed to the occurrence of a medication error and which should be taken into account for case follow-up.

4.5. Complementary guidance

This guidance should be read in conjunction with the following EU and international guidance:

- GVP Module V (rev. 1) on risk management
- GVP Module VI (rev. 1) on the management and reporting of adverse reactions to medicinal products
- GVP Module VII (rev. 1) on Periodic Safety Update Report
- ICH E2B (R3) Implementation Guide for Electronic Transmission of Individual Case Safety Reports
- ICH E2C (R2) Periodic Benefit Risk Evaluation Report (PBRER) the contents of which are consistent with GVP Module VII Periodic Safety Update Report
- ICH E2F Development Safety Update Report (DSUR)[4]
- ICH-Endorsed Guide for MedDRA Users: MedDRA® Term Selection: Point to Consider (latest version)

[4] ICH E2F guidance on Development Safety Update Reports (DSUR) requires that for an investigational medicinal product which has been approved for marketing in any country, safety findings from marketing experience relating to the approved indication but also on off-label use, administration to special populations (e.g. pregnant women), medication errors, overdose and abuse are included. Relevant points to consider for the evaluation of risks include (where applicable) evidence of clinically significant medication errors.

5. Structure and processes

This chapter highlights the general principles in relation to the recording, coding, reporting and assessment of medication error reports associated with medicinal products for human use, which are applicable to competent authorities responsible for medicinal products in EU Member States and marketing authorisation holders. The definitions provided in chapter 4. should be followed. EU requirements are presented in chapter 6.

5.1. Recording of medication error reports

In line with the scope of this guidance, recording medication errors associated with suspected adverse reaction(s) in the context of EU pharmacovigilance obligations applies to competent authorities in the EU Member States, marketing authorisation holders and the Agency, and includes the collection and collation of such case reports.

EU Member States are required by Article 102 of Directive 2001/83/EC to encourage healthcare professionals and consumers to report suspected adverse reactions to national competent authorities. Medication errors associated with the use of a medicinal product which result in harm may be reported spontaneously as unsolicited communication by a healthcare professional or consumer to a competent authority, a marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre, etc.). In this context GVP VI.A.2.3 defines a healthcare professional as a medically-qualified person such as a physician, a dentist, a pharmacist, a nurse, a coroner or as otherwise specified by local regulations. A consumer is a person who is not a healthcare professional i.e. a patient, a lawyer, or a friend, a relative or a carer of a patient.

If the error is associated with adverse reaction(s), the legal requirements for recording, reporting and assessment of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the EU as detailed in Title IX 'Pharmacovigilance' of Directive 2001/83/EC and Chapter 3 of Regulation (EC) No 726/2004 apply. Marketing authorisation holders and national competent authorities should therefore record medication errors associated with adverse reaction(s) as ICSR in ICH E2B format in the local (MAH) or national (NCAs) pharmacovigilance database.

It is good practice to also record cases of medication errors not associated with adverse reaction(s) in the format of an ICSR, however these cases should not be reported as valid individual cases in accordance with GVP VI (see chapter 5.3.). Marketing authorisation holders and national competent authorities may use alternative formats as appropriate or if required by national legislation to record cases.

From a patient safety perspective, errors in treatment and care may be the result of faulty procedures or systems and may or may not involve the use of medicines. Such errors may be reported spontaneously by healthcare professionals or consumers to the local healthcare provider organisation (e.g. a hospital, a nursing home, a general practitioner) where the patient has been treated. Such cases may be recorded and reported as 'patient safety incident' to regional and/or national patient safety organisations (PSO) where they exist in EU Member States.

Patient safety incident reports involving an error in the use of a medicine which are associated with adverse reaction(s) brought to the attention of a national patient safety organisation should also be *made available* to the competent authorities in EU Member States responsible for the supervision of medicines (see also chapter 6.2.).

In line with the ICH E2C (R2) guideline and GVP Module VII.B.5.9 on PSURs, marketing authorisation holders should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes, in the PSUR sub-section on medication errors for the interpretation of safety data and for the benefit-risk evaluation of medicinal products.

In addition, GVP module V on risk management systems requires that the potential for medication errors is addressed in module SVI 'Additional EU requirements for the safety specification' providing cumulative data.

For the purposes outlined above marketing authorisation holders should therefore record, report and assess all medication errors which are brought to their attention, regardless of whether associated with an adverse reaction(s), in their pharmacovigilance system or equivalent system for medication error reports not associated with adverse reaction(s). This should allow the generation of summary tabulations and of listings of individual cases to support assessment (see chapter 5.4. and 6.5.), and apply the classification described in chapter 4.3.2. of this guidance. Based on this classification, table 1 below provides an overview how medication errors are recorded both from a pharmacovigilance and patient safety perspective. In addition, table 1 shows the reporting requirements for marketing authorisation holders in line with EU pharmacovigilance obligations and GVP recommendations.

Table 1: Recording medication errors occurring in the EU.

			Patient Safety	Pharmacovigilance	
Medication Error Type	Error Occurred	Harm (ADR)	Recording	Recording	Report Type
Error with ADR	✓	✓	Incident with harm	Medication error with clinical consequence(s)	ICSR reportable to NCA and/or EV[3]; PSUR summary[1]; RMP;
Error Without Harm	✓	×	Incident	Medication error without clinical consequence(s)	PSUR summary[1]; RMP;
Intercepted Error	✓	N/A	Prevented incident ('near miss')	Intercepted medication error	PSUR summary[1]; RMP;
Potential Error	×	N/A	N/A[2]	MedDRA PTC: use of Term 'Circumstance or information capable of leading to medication error'	PSUR summary[1]; RMP;

✓ Indicates event did happen; × indicates event did not happen; N/A not applicable; EV EudraVigilance

[1] The PSUR summary information includes interval and cumulative summary tabulations in line with GVP VII, and on request of the competent authority or the Agency additional listings of cases of medication error of special interest relevant for the benefit-risk evaluation. See chapters 5.3. and 5.4.

[2] Not in line with the definition of a patient safety incident which is any unintended or unexpected incident which could have or did lead to harm for one or more patients receiving e.g. NHS England care. Report prevented patient safety incidents (known as 'near misses'). Therefore a potential error is not an incident because it has not occurred and is not a near miss because it cannot be said that it has been prevented.

[3] Only applicable after successful EudraVigilance audit, see chapter 5.3. and Annex 1.

5.2. Terminologies for coding purposes

In line with the scope of this guidance the terminology stakeholders will use for recording and coding medication errors will depend on the purpose, i.e. compliance with EU pharmacovigilance reporting requirements or compliance with national, regional or local patient safety reporting systems where established in EU Member States. This chapter briefly describes the terminologies applied to either context.

5.2.1. Context of pharmacovigilance

The Medical Dictionary for Regulatory Activities (MedDRA) is used worldwide by regulatory authorities, pharmaceutical companies, clinical research organisations and health care professionals for sharing information concerning medicinal products for regulatory purposes.

In line with Article 25 of the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities, the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, EU Member States, marketing authorisation holders and the Agency shall apply the MedDRA terminology.

The definition of medication error provided in chapter 4.3. is close to the definition provided in the MedDRA Term Selection: Point to Consider (MTS:PTC) and introductory guide. Subcategories of medication errors covered by this definition would include *prescribing errors* of physicians or other healthcare professionals who have the authority to prescribe, or *dispensing errors* which are not limited to pharmacists, but may also include nurses and physicians who dispense medicines. Also *documented hypersensitivity to administered drug* is a subcategory of medication error referring to the situation when a patient is administered a medicinal product that is documented in the patient's medical file to cause a hypersensitivity reaction in the patient.

The concept of intercepted errors referred to in chapter 4.3.3. is also reflected in MedDRA providing several terms for coding and data retrieval purposes under the *HLT Medication Errors NEC*. For further information please refer to MTS:PTC.

Medication errors should be clearly distinguished from *off-label use* which according to GVP module VI refers to situations where the medicinal product is *intentionally* used for a medical purpose not in accordance with the authorised product information.

Medication errors should be distinguished from *misuse*, which is defined as *intentional and inappropriate* use of the medicinal product not in accordance with the authorised product information.

Also *product quality issues* which are abnormalities that may be introduced during the manufacturing/labelling, packaging, shipping, handling or storage process of a medicinal product should be distinguished and not included in the definition of a medication error provided in chapter 4.3. of this guidance. For example, the splitting of a scored tablet in two differently sized parts is considered a product quality complaint and not a medication error.

5.2.2. Context of patient safety

Errors may happen when patients receive healthcare services for preventive, diagnostic, curative or rehabilitative purposes which may or may not involve the use of a medicine. If medication errors happen with a pattern or at an unacceptable frequency or result in serious consequences for the patient and public health, it is essential to understand the causes, contributory factors as well as

consequences of the error, and the possible mitigating actions and solutions which could prevent the error from happening again.

There is currently no commonly agreed terminology used for classifying patient safety incident reports in national reporting and learning systems of EU Member States where they exist.

The World Health Organization (WHO) has been leading in examining patient safety incident reporting and learning systems. A major milestone was the launch of the Conceptual Framework for the International Classification for Patient Safety (WHO ICPS) as the basis for a common language. WHO ICPS defines an error as a failure to carry out a planned action as intended or application of an incorrect plan. Errors may manifest by doing the wrong thing (commission) or by failing to do the right thing (omission), at either the planning or execution phase. In the context of medication practice the plan or intended action is directed towards successful treatment of the patient's condition.

To facilitate learning from patient safety incident reports, WHO is currently undertaking work aimed at drafting a Minimal Information Model (WHO MIMS) which will be universally applicable to patient safety incident reporting. For more information please refer to the WHO website.

5.3. Reporting requirements for medication errors associated with adverse reactions

Medication errors associated with adverse reaction(s) may be reported spontaneously as unsolicited communication by a healthcare professional or consumer to a competent authority, a marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre) or described in the scientific literature.

GVP module VI.C.6 highlights the requirements for the electronic exchange of information on medication errors associated with adverse reaction(s) between competent authorities in EU Member States, marketing authorisation holders and the Agency through EudraVigilance, the data processing network to collate and share pharmacovigilance information electronically as defined in Articles 24(1) and 24(3) of Regulation (EC) No 726/2004.

Medication errors may also be reported in the context of solicited reports of suspected adverse reactions derived from organised data collection systems, which include clinical trials, observational studies, registries etc. The general reporting rules for suspected adverse reactions occurring in organised data collection systems conducted in the EU under the scope of Directive 2001/83/EC, Regulation (EC) No 726/2004 or Regulation (EU) No 536/2014[5] apply accordingly. Figure 3 outlines the information flow for medication error reporting in line with EU pharmacovigilance reporting requirements of Directive 2001/83/EC and taking into account the role of national patient safety organisations as referred to in Article 107a(5) of Directive 2001/83/EC.

[5] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

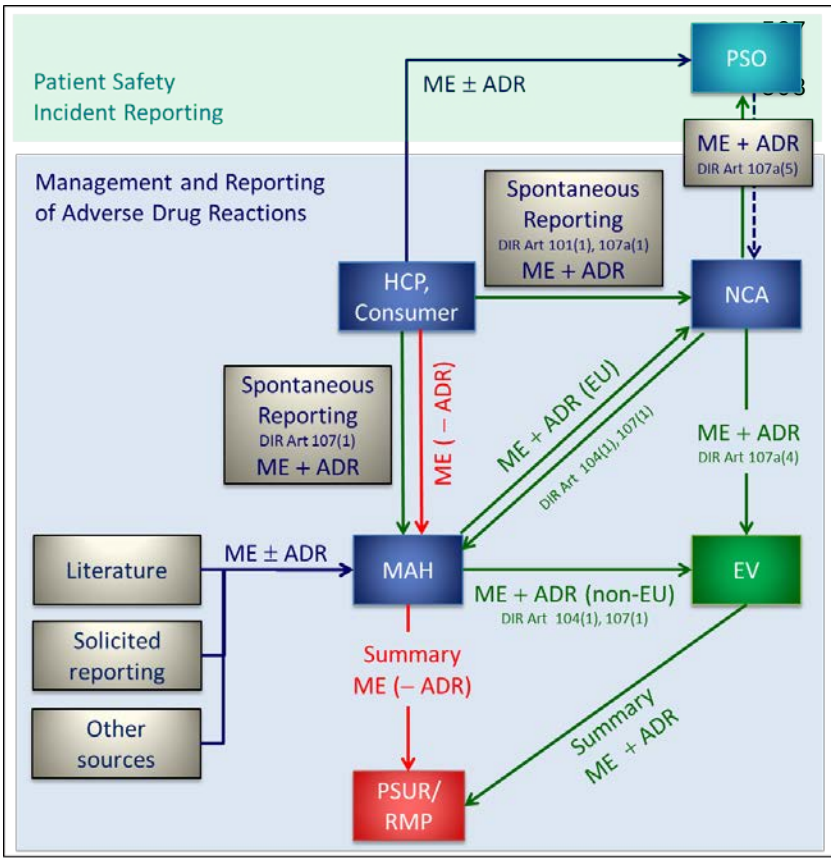


Figure 3: The graph shows the information flow (green arrows) for medication errors reports associated with suspected adverse reaction(s) (+ ADR) in line with EU reporting requirements of Directive 2001/83/EC, and the stakeholders involved: marketing authorisation holders (MAH), national competent authorities (NCA) and authorities, bodies, organisations and/or institutions responsible for patient safety (PSO) where they exist within a Member State in accordance with Article 107a(5) of Directive 2001/83/EC. The red arrows represent medication error reports not associated with suspected adverse reactions (– ADR) brought to the attention of MAHs and/or NCAs which are outside the scope of EU reporting requirements of Directive 2001/83/EC and should therefore not be submitted as ICSR, however such reports should be included as summary information in periodic safety update reports (PSUR) and risk management plans (RMP) in line with GVP. From a public health perspective, it is good practise that NCAs in Member States are also informed of adverse reactions associated with medication errors which have been brought to the attention of a PSO in that EU Member State (dotted line).

Annex 1 provides the above information flow reflecting the simplified adverse reaction reporting rules in accordance with Regulation (EC) No 726/2004 which will enter into force six months after the announcement by the EMA Management Board that based on an independent audit report, the EudraVigilance database has achieved full functionality in line with the provisions of Article 24(2) of Regulation EC No 726/2004.

For the purpose of this guidance as shown in figure 4, all reports of suspected (serious and non-serious) adverse reaction(s) associated with medication errors should be reported by MAHs and competent authorities in EU Member State as individual case safety reports in line with definition provided in GVP VI.A.2.5 and the requirements detailed in GVP Module VI.C.3 and VI.C.4 regarding reporting time frames and reporting modalities. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product in order to be reportable to competent authorities (GVP VI.B.2). In addition, the

reporting requirements for ICSRs to EudraVigilance apply, please refer to GVP VI.C.4 'Reporting modalities for serious and non-serious ICSRs' in connection with GVP VI Appendix 3.

Figure 4: MAHs and NCA reporting requirements for spontaneous reports of suspected (serious and non-serious) adverse reaction(s) associated with medication errors.

In line with the provisions of GVP Module VII.B.5 the PSUR includes cumulative and interval summary tabulations of data relevant for the benefit-risk evaluation of a medicinal product, including data on medication errors associated with spontaneous (serious and non-serious) adverse reaction reports (ISCRs) from post-marketing data sources. This includes reports from healthcare professionals, consumers, scientific literature, competent authorities and from solicited non-interventional studies, as well as medication errors which may constitute for example a safety signal or a safety concern. Serious adverse events from clinical trials and serious adverse drug reactions from non-interventional studies and other non-interventional solicited sources associated with medication errors may also be included in the relevant PSUR sections.

Once the EudraVigilance database has achieved full functionality following a successful audit and is accessible to marketing authorisation holders to the extent necessary to comply with their pharmacovigilance obligations[6], summary tabulations from EudraVigilance supporting the assessment of medication errors in PSURs may be created using reports by means of the EudraVigilance data analysis system and complemented with additional data on medication errors held in the marketing authorisation holder's own pharmacovigilance system (i.e. non-serious cases of medication errors which occurred outside the EEA and medication errors not associated with adverse drug reactions). Alternatively marketing authorisation holders may create summary tabulations from their own pharmacovigilance system provided the system contains all relevant information on medication errors. A report on medication errors will also be made available on the European database on suspected adverse drug reaction reports (www.adrreports.eu) in line with the revised EudraVigilance access policy[7].

In line with the provisions of GVP VII.C.4.2.2, the assessment of the causes and circumstances that led to a medication error may be supported by additional listings of individual cases of medication errors of special interest upon request by the competent authority or the Agency. Listings of individual cases should be provided by the marketing authorisation holder within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual cases of medication errors associated with adverse reaction(s) where necessary for the scientific evaluation, including information on numbers of serious cases, details on the causes and circumstances that led to the medication error, mitigating and ameliorating factors and as necessary, analysis of non-serious cases. The MedDRA coding principles in section 5.6. should be applied.

A template for summary tabulation and additional listing of individual cases of medication errors of special interest upon request is provided in Annex 2.

[6] Article 24(2) of Regulation (EC) No 726/2004.
[7] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf

5.3.1. Medication errors related to invented names

The checking of invented names is part of the EMA's role in evaluating the safety of medicinal products within the centralised authorisation procedure, since the proposed invented name(s) could create a public health concern or potential safety risk. Regardless of the association with adverse reaction(s) medication errors related to the invented name of a medicinal product (e.g. product name confusion) should be notified to the Agency's Name Review Group via the dedicated mailbox (nrg@ema.europa.eu) for centrally authorised products. The guideline on the acceptability of names for human medicinal products processed through the centralised procedure (EMA/CHMP/287710/2014 – Rev. 6) applies. For nationally authorised medicinal products competent authorities in Member States should be contacted for national guidance on checking invented names.

For ICSRs reporting a name confusion, the names of both medicinal products involved in the confusion should be provided in the drug section regardless whether the sender holds a marketing authorisation for both products. In ICH E2B (R3) format the product which the patient received by mistake should be given the drug characterisation 'suspect' and the product which was not received (because of the error), should be assigned the characterisation 'drug not administered'. The coding for 'additional information on drug' should also be applied as outlined in section 5.5.2. The MedDRA terms selected should indicate the name confusion and any other associated medication errors and adverse reactions.

5.4. Periodic reporting of medication errors without an adverse reaction

Information on medication errors where no suspected adverse reaction has occurred, or in other words where the error did not result in clinical consequences or harm to the patient, do not fall in the definition of a reportable individual case provided Article 1(11) of Directive 2001/83/EC.

By analogy, intercepted errors (see definition 4.3.3.) and potential medication errors (see definition 4.3.4.) which may occur in the context of the use of a medicinal product are not reportable as individual case safety reports to competent authorities responsible for medicinal products or to EudraVigilance. However, it is good practice that competent authorities systematically record information about medication errors without adverse reaction(s) which may be brought to their attention through exchange agreements with national patient safety organisations as outlined in chapter 6.2.

The information on medication errors without suspected adverse drug reaction brought to the marketing authorisation holder's attention may be relevant for the scientific evaluation and interpretation of safety data and of the overall benefit-risk profile of the medicinal product and should therefore be systematically recorded and assessed by marketing authorisation holders for pharmacovigilance purposes.

In line with the recommendations of GVP Module VII, patterns of medication errors regardless of whether associated with adverse reaction(s) should be included as summary information in the PSUR sub-section VII.B.5.9 2. on 'Medication errors' as shown in figure 5.

Marketing authorisation holders should make all reasonable efforts to include in the PSUR summary relevant information on patterns of medication errors, taking into account the reports brought to their direct attention by healthcare professionals and consumers and those published in the scientific literature, in addition to information either made public as single case reports, listings of individual cases or otherwise aggregated data or evaluations from national competent authorities and patient safety organisations if not presented elsewhere in the PSUR.

To support the assessment of the causes and circumstances of medication errors brought to the MAH's attention which are not associated with adverse reaction(s) including intercepted and potential errors,

listings of individual cases should be provided upon request by the competent authority or the Agency if the medication errors constitutes an area of special interest with relevance for the overall benefit-risk evaluation of the medicinal product (e.g. where a signal has arisen) or if the medication error is a safety concern in the risk management plan. A template for additional listings of individual cases of medication errors of special interest upon request is provided in Annex 2.

For the purpose of reporting medication errors in PSURs, marketing authorisation holders should apply the classification proposed in chapter 4.3.2. accordingly.

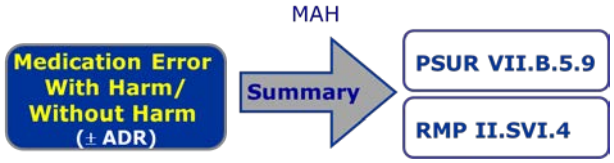


Figure 5: GVP requires MAHs to summarise information on patterns of medication errors in PSUR and RMP regardless of whether associated with adverse reaction(s).

PSUR section VII.B.5.9 should also include cross-references to other relevant PSUR sections (see chapter 5.3.) where case reports of medication errors associated with an adverse reaction are discussed.

If the medication error constitutes an important safety concern which impacts on the overall benefit-risk balance of the medicinal product or on public health, such case regardless of whether associated with an adverse reaction should be notified in line with the recommendations of GVP Module VI.C.2.2.6 as an emerging safety issue to National Competent Authorities and the Agency via a dedicated mailbox: P-PV-emerging-safety-issue@ema.europa.eu.

In line with the recommendations of GVP Module V.B.8.6.4, the risk management plan Part II, Module SVI.4 “Potential for medication errors” should include a stand-alone summary of aggregated data on medication errors which occurred during the clinical trial programme and/or post-marketing period regardless of whether associated with adverse drug reaction(s), as shown in figure 5. The following information should be provided based on the summary tabulations or listings of individual cases provided in the PSUR (see Annex 2):

- Description of error (i.e. type or category as applicable)
- Number of occurrences up to data lock point
- Analysis of cause (based on the parameters described in chapter 5.5.1.)
- Steps taken to prevent the error
- Comments

Where available, the information from failure mode and effects analysis (FMEA) conducted during the development programme for new medicines should be taken into account to evaluate the risk of medication errors in normal clinical practice and to identify knowledge gaps in the safety profile where additional pharmacovigilance activities may be required. FMEA may be able to detect issues related for example to the invented name, product presentation, labelling, product user groups, translation into Braille or accidental ingestion by children.

5.5. Follow-up of medication error reports

GVP module VI.B.3 provides detailed guidance on how ICSRs should be followed-up to obtain as comprehensive information as required for the scientific evaluation and causality assessment of the reported case, in addition to any effort to collect the minimum information for an ICSR to be valid (please refer to GVP VI.B.2). GVP VI.B.2 also provides that reports, for which the minimum information for a valid ICSR remains incomplete, should nevertheless be recorded within the pharmacovigilance system to support on-going safety or benefit-risk evaluation activities.

Where medication errors are monitored events of special interest (e.g. where a signal has arisen) or safety concerns in the risk management plan of a medicinal product, or where the error resulted in serious harm to the patient, as a general rule the case should always be followed-up with the primary reporting source.

5.5.1. Parameters to follow-up when reporting medication errors

To ensure better learning from medication errors for the development and promotion of safe medication practice, it is good practice that marketing authorisation holders and national competent authorities follow-up essential information in relation to medication errors brought to their attention regardless of whether the error was associated with adverse reaction(s). Table 2 below provides an overview of parameters which may support the scientific evaluation of individual case reports or of aggregated data on medication errors.

For medication errors which are associated with serious adverse reaction(s), marketing authorisation holders and national competent authorities should make all reasonable efforts to collect the essential information provided in table 2 through appropriate case follow-up, unless national requirements for anonymous reporting of medication errors prevent follow-up.

It is good practice that national competent authorities perform follow-up activities in collaboration with national patient safety organisations based on the exchange agreements for information and reports on medication errors referred to in chapter 6.2.

Contributing factors are particularly relevant for the analysis of root causes which led to the error (see chapter 4.4.) and should be discussed in the relevant PSUR sections (e.g. GVP VII.B.5.9) to support the assessment of signals and the selection of adequate risk minimisation measures intended to prevent or reduce the occurrence of medication errors in RMPs. Follow-up is particularly important to enable learning from cases with a potential for harm to the patient and from cases involving errors of omission resulting in adverse reaction(s). Table 2 also provides guidance on the respective ICH E2B ICSR data elements where the essential follow-up information should be reported in an ISCR.

Case reports of medication errors should include where possible the following information:

- Category (type) of medication error (see chapter 4.3.2.)
- Stage of medication process where the error occurred
- Contributing factor(s)
- Reported adverse reaction(s) if the error affected the patient or consumer with clinical consequences (error with ADR)
- Potential risk(s) for the patient or consumer if the error did not happen (potential error) or did not reach the patient or consumer (intercepted error, error without harm)
- Medicinal product(s) involved

705 • Batch number if the error is due to device failure

706 Table 2: Parameters to follow-up when reporting medication errors

Parameter	Description	ICSR Data element E2B (R2)	ICSR Data element E2B R(3)
Setting	Inpatient (hospital, nursing home, care home), outpatient (general practitioner, specialist practice, ambulatory), pharmacy, drug store, private home, etc. Since this information is sensitive due to possible legal implications in the context of HCP liability, anonymisation of HCP personal data should be guaranteed, see chapter 5.7.1.)	A.2 Primary source B.5 Narrative (Narrative information should only provide general setting not reporter information)	C.2.r Primary source H.1 Narrative H.5 Case narrative in native language (Narrative information should only provide general setting not reporter information)
Stage of medication process	If NOT clearly derived from MedDRA coded reaction term(s) (single term or combination of terms), the stage of the medication process where the error occurred should be provided in the narrative: • Prescribing • Dispensing • Preparation for administration • Administration	B.5 Narrative	H.1 Narrative H.5 Case narrative in native language
Category (type) of medication error	The appropriate MedDRA LLT term(s) (either single term or combination of terms) (see chapter 5.6.) should be selected to reflect the category (type) of error.	B.2.i.1.b Reaction/ event in MedDRA terminology B.5.3.b Sender's diagnosis	E.i.2.1 Reaction/event H.3.r.1.b Sender's diagnosis
	If the type of error cannot be coded with a specific MedDRA LLT term, the LLT 'Medication error' should be used and further detail on the category (type) of medication error should be provided in the narrative.	B.2.i.1.b Reaction/ event in MedDRA terminology B.5 Narrative	G.k.10.r Additional information on drug H.1 Narrative case summary and

Parameter	Description	ICSR Data element E2B (R2)	ICSR Data element E2B R(3)
			further information H.5 Case narrative in native language
Contributing factor(s)	Covariates, actions or influences which are thought to have played a part in the origin or the development of the medication error (or to increase the risk of error) related to: • Patient or healthcare professional staff related human factors such as behaviour (e.g. distraction, fatigue), performance (e.g. breach of standard of care) or communication issues (e.g. illegible handwriting on prescriptions, discharge recordings); • Work, e.g. system factors such as work environment, staffing issues, workload, shift work; • Organisation, e.g. healthcare policy, transition of patient care; • External factors beyond the control of the healthcare professional or patient , e.g. medication unavailability; This information may be provided by the primary reporter, or if the information is missing the ICSR sender should perform case follow-up. This is necessary information to conduct root cause analysis (see 4.4.) where appropriate.	B.5.2 Reporter's comments B.5.4 Sender's comments	H.1 Narrative case summary and further information H.2 Reporter's comments *or* H.4 Sender's comments H.5 Case narrative in native language
Medicinal product(s) involved	The medicinal product information should be coded in the ICSR drug section. If the patient did not receive the actual prescribed drug but another one, in ***E2B (R3)*** repeatable ICSR sections G should be completed with the information about the prescribed drug and the term '*Drug not administered*', as well as the information on the dispensed drug as the 'suspect' drug. In ***E2B (R2)*** the free text field 'additional information on drug' can also be used. The medication error should be captured with the appropriate MedDRA LLT code in section E.i Reaction(s)/Event(s).	B.4.k Drug information B.4.k.1 Characterisation of drug role B.4.k.19 Additional information on drug	G.k.1 Characterisation of drug role + G.k.2 Drug identification + G.k.10.r Additional information on

Parameter	Description	ICSR Data element E2B (R2)	ICSR Data element E2B R(3)
	The additional information on drug (coded) data element G.k.10.r should be populated (*7=medication error*) for E2B (R3).		drug
Covariates defining the treated population (CIOMS V)	• For paediatric population: consider factors linked to the need for individualised doses depending on age, weight and body surface area, age-related weight increase over time; lack of inadequate information in the SmPC and PIL for dose calculation and of appropriate paediatric formulations; specific drug combinations in neonates, transitions of care such as admission and discharge. • For the elderly: consider higher risk of inappropriate prescribing associated with multiple morbidities and poly-pharmacy, medication reconciliation issues, poor adherence to treatment regimen (e.g. through impaired vision product label/PIL cannot be read) and increased susceptibility to ADRs e.g. through renal and hepatic functional decline. • Disease/Condition: indication treated, disease severity, acute/chronic, co-morbidities • Relevant medical history: risk factors, diet, alcohol use, tobacco use, concomitant therapy/treatment • Pharmacology-related: blood or tissue levels; pharmacodynamic, pharmacokinetic and pharmacogenetic information • Miscellaneous: prescriber (generalist vs specialist), pregnancy/nursing status, organ impairment	B.5 Narrative case summary and further information B.5.2 Reporters comments B.5.4 Senders comments B.1.7 Medical history B.3 Tests B.4 Concomitant drugs	H.1 Narrative case summary and further information H.2 Reporter's comments *or* H.4 Sender's comments D.7.1.r.5 Comments +/- D.7.2 Text for relevant medical history and concurrent conditions +/- D.8 Relevant past drug history F.r.2.2.b Test name
Patient outcome	Patient outcome should be recorded for each MedDRA term coded. Strictly speaking the outcome of a medication error is not applicable if the medication error did occur. As this outcome is not available in E2B, the outcome should match the outcome of the consequential suspected ADR.	B.2.i.8 Outcome of reaction/ event at the time of last observation	E.i.7 Outcome of reaction/event at time of last observation
Seriousness	Coded according to ICSR seriousness criteria (refer to GVP VI.A.2.4 seriousness criteria: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant		E.i.3.2 Seriousness criteria at event level

Parameter	Description	ICSR Data element E2B (R2)	ICSR Data element E2B R(3)
	disability or incapacity, is congenital anomaly/birth defect) for serious adverse drug reactions. For medication errors associated with non-serious adverse drug reaction(s) the patient outcome should be reported accordingly.		
	For medication errors without ADR (i.e. intercepted errors, errors not resulting in harm, potential errors) the potential for harm should be described in the narrative of the case in the organisation's database. These reports are not reportable in the EU.		H.1 Narrative case summary and further information
Mitigating factors	Actions or circumstances which prevented or moderated the progression of an error towards harming the patient. Such actions could be taken with the medicinal product as a result of the reaction(s)/event(s), e.g. drug withdrawn, dose reduced, dose increased, etc. There may be other mitigating actions or circumstances which should be reported in the narrative accordingly.	B.5 Narrative case summary and further information + B.4.k.16 Action(s) taken with drug	G.K.8 Action(s) taken with drug +/- H.1 Narrative case summary and further information
Ameliorating factors	Corrective actions which took place after the medication error has already caused harm to the patient. Such actions could be taken with the medicinal product as a result of the reaction(s)/event(s), e.g. drug withdrawn, dose reduced, dose increased, etc. There may be other corrective actions or circumstances which should be reported in the narrative accordingly, e.g. administration of an antidote.	B.5 Narrative case summary and further information + B.4.k.16 Action(s) taken with drug	G.K.8 Action(s) taken with drug +/- H.1 Narrative case summary and further information

If the information about a medication error received directly from a consumer/patient is incomplete, attempts should be made to obtain the consumer/patient's consent to contact a nominated healthcare professional to obtain further follow-up information. When the occurrence of the reaction/event of such case, initially reported by a consumer/patient, has been confirmed (totally or partially) by a healthcare professional, this information should be highlighted accordingly in the report.

Follow-up of medication error cases should be tailored towards optimising the collection of important missing information which may in exceptional cases involve targeted questionnaires in local language. Marketing authorisation holders are encouraged to discuss the content of medication error specific follow-up questionnaires with national competent authorities and to provide a copy in the risk management plan Annex 7 as appropriate.

5.5.2. ICH E2B (R3) 'Additional information on drug' data element

For the new ICH E2B (R3) standard options for medication error flagging are available. For the current ICH E2B (R2) standard please refer to GVP VI.

ICH E2B (R3) - Additional Information on Drug (coded) (G.k.10.r)

The ICH E2B (R3) standard for the electronic transmission of ICSRs provides the option of coding additional information which is not covered elsewhere in the E2B (R3) data elements under the data element 'Additional Information on Drug (coded) (G.k.10.r)' in order to 'flag' medication errors at drug level using code 7 which stands for medication error. The case details still have to be MedDRA coded in the relevant data fields as described in chapter 5.6. In this data element further scenarios may be coded which are however outside the scope of this guidance. A business process for using ICH E2B (R3) for recording medication errors in ICSRs is provided in Annex 4.

There may be situations where in this data element more than one code can be selected, for example if a medication error led to unintentional overdose both codes for the medication error (code 7) and for the overdose (code 2) should be selected. In addition to the flag, a MedDRA Lowest Level Term (LLT) should also be provided in data element Reaction(s)/Event(s) (E.i.2.1) selecting the most specific code possible to provide details on the type of medication error at case level, and where this information cannot be coded it should be provided in the narrative (H.1). In addition, data element G.k.11 can be used to provide further information in free text format where it cannot be specified by G.k.10.

ICH E2B (R3) - Characterisation of drug role G.k.1

For medication errors where the patient did not receive the actual prescribed medicinal product but another medicinal product, repeatable 'Sections G' should be completed with the information about the prescribed drug (selecting the characterisation of drug role as 'drug not administered'), as well as the information on the dispensed drug as the 'suspect' drug. The appropriate medication error should be captured with the appropriate MedDRA Lowest Level Term (LLT) code for the associated reaction/event in data element Reaction(s)/Event(s) (E.i.2.1).

Inferred medication errors

There may be instances where the initial primary reporter has not specifically stated there was a 'medication error' but it is clear from the information provided that there has been an error. MedDRA coding principles advise that medication errors should not be inferred unless specific information is provided.

For cases clearly associated with a medication error based on specific information but where the term 'medication error' has not been stated by the primary source, marketing authorisation holders and national competent authorities potentially exposed to liability in accordance with EU Member States' national law may provide a disclaimer (see chapter 5.7.) in the 'senders comment' section.

5.6. Coding medication errors with MedDRA

To ensure consistency in how MedDRA terms are assigned to *verbatim* reports of medication errors and related information on the type of error, its causes (i.e. contributing factors related to human behaviour), clinical consequences (i.e. adverse reactions), symptoms and diseases, this guidance should be read in conjunction with the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' (MTS:PTC) document. The MTS:PTC guide promotes accurate and consistent term selection and can be downloaded from the MedDRA website. The MTS:PTC guide should also be used by healthcare professionals, researchers, and other parties (e.g. patient safety

organisations) involved in the reporting of medication errors. The focus of the current MedDRA terminology is on coding clinical consequences of medication errors but to support the analysis of the causes why the error occurred in the first instance. Discussions on the expansion of MedDRA e.g. to include human use factors are ongoing.

5.6.1. General coding principles

GVP Module VI, chapter VI.C.6.2.3.3 on “suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupational exposure” provides that if a case of medication error is reported with clinical consequences, the MedDRA Lowest Level Term (LLT) code, corresponding to the term closest to the description of the reported medication error should be added to the term for the suspected adverse reaction(s) in the data element ‘Reaction/event in MedDRA terminology (Lowest Level Term)’ (ICH-E2B(R2) B.2.i.1), in line with the recommendations of MTS:PTC in its latest version.

As a guiding principle MedDRA coders should only code what can be read in the report, without adding or subtracting any information, and coders should not infer a medication error unless specific information is provided by the primary source (the same principle applies to intentional overdose, off-label use, misuse and abuse). In line with GVP VI.C.2.2.3 where a competent authority or marketing authorisation holder disagrees with the diagnosis reported by the primary source, an alternative diagnosis can be provided in the ICH-E2B (R2) data element B.5.3 ‘Sender's diagnosis/syndrome and/or reclassification of reaction/event’ in addition to the reported diagnosis provided in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.
For the purpose of summarising medication error reports in PSUR and RMP, the MedDRA structure allows for aggregation of reported terms in medically meaningful groupings to facilitate analysis of safety data. MedDRA can also be used to produce summary tabulations or listings of individual cases as referred to in chapter 5.4. to compute frequencies and to capture and analyse related data such as indications, investigations, medical and social history.

5.6.2. Special situations

This chapter provides guidance for MedDRA coders in special situations which may be associated with medication errors.

a) Is intentional re-challenge considered a medication error?

The concept of challenge, de-challenge and re-challenge to a medicinal product is one of the standard means of assessing adverse reactions. The administration of a suspect product to a patient, its subsequent withdrawal from the patient’s regimen with partial or complete disappearance of an adverse reaction (positive de-challenge) and subsequent reintroduction of the suspected product is by definition an intentional process. Therefore intentional re-challenge to a medicinal product should not be considered a medication error and not be coded as such.

b) Differences in term selection from *HLT Maladministrations* vs *HLT Medication Errors NEC*

There are some differences in selecting terms from the two HLTs. As the name suggests the maladministration HLT terms are associated with errors in administration. A term in the *HLT Medication Error NEC* may indicate that there was an error but not specify that it ended up as an administration error.

Some terms may require some consideration e.g. 'Wrong patient received medication' versus 'Drug dispensed to wrong patient'. The latter is a dispensing error which may or may not have reached the

patient whereas the other term clarifies that the patient received the medication but the term does not specify the stage at which the error occurred.

c) Coding at different stages of medication error

Medication errors can be a series of events as shown in figure 2 at prescribing, dispensing, preparation or administration. As shown in chapter 4.3.2. there may be more than one stage in the drug treatment process where for example a prescription error if not intercepted would lead to a dispensing error, and consequently result in an administration error.

Other than monitoring errors, all medication errors which reach the patient are de facto administration errors. For coding purposes it is most important to capture the primary point in the chain of events. It is preferable to code other downstream errors in addition to provide as much information as possible.

d) Treatment non-compliance of the patient

Patient non-compliance with prescribed treatment or course of medication may result from a variety of factors with the most common scenarios being:

- *Intentional non-compliance* if the patient decides not to take the prescribed medicine because he feels better (e.g. antibiotic course not completed);
- *Medication error* if the patient is not capable of complying without supervision (e.g. Alzheimer's patient forgets to take drug or patient treated with antipsychotics);

In general if there is an element of intention implied, similar to the concept of intentional overdose/underdose and off-label use described in chapter 5.6.6. , this would be outside the scope of a medication error. The example of a patient not completing the course of antibiotics may be considered a misuse in accordance with the definition in GVP VI.

Circumstances of treatment non-compliance which cannot be coded with appropriate MedDRA terms should be provided in the narrative.

e) Medicinal product unavailability

If a patient is unable to get a (repeat-) prescription (e.g. from pharmacy or from emergency supplies) or due to a manufacturing defect and as a consequence the patient experiences a deterioration of the underlying condition, this is not considered a medication error. In this context MAHs should consider notification of any withdrawal, suspension or cessation of marketing of a human medicinal product to the competent authority as applicable[8].

5.6.3. MedDRA term selection

The latest version of MedDRA terminology (www.meddra.org) should always be used and corresponding changes to the MedDRA term hierarchy taken into account. Within the *SOC Injury, poisoning and procedural complications* the *HLGT Medication Error*s provides HLTs which are most relevant for coding medication errors.

The MedDRA Introductory Guide (http://www.meddra.org/how-to-use/support-documentation) provides concept descriptions of MedDRA Preferred Terms (PT) for interpretation and coding purposes. Other relevant terms may be included under other MedDRA SOCs. It is recommended to use the MedDRA browser to identify available terms.

[8] For further information please refer to Q&A on withdrawn-product notifications: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000143.jsp&mid=WC0b01ac0580745911

The ICH-endorsed guide for MedDRA users 'MedDRA Term Selection: Points to Consider' (MTS:PTC) document provides comprehensive guidance including examples of how medication errors should be coded in the following scenarios and the MTS:PTC latest version should always be consulted.

If a case of medication error is reported with clinical consequences, the MedDRA Lowest Level Term (LLT) codes, corresponding to the term closest to the descriptions of both the reported medication error and the clinical consequences should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1 or ICH-E2B(3) E.i.2.1), in line with recommendations included in the latest version of the MTS:PTC.

Annex 3 provides additional coding examples for medication errors complimentary to the MTS:PTC.

5.6.4. Accidental and occupational exposures versus medication error

In GVP VI.A.2.1.2 occupational exposure refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation. For the purposes of MedDRA term selection and analysis of MedDRA-coded data, the MedDRA Introductory Guide version 17.0 encompasses under occupational exposure the 'chronic' exposure to an agent (including therapeutic products) during the normal course of one's occupation, and could include additional scenarios in specific regulatory regions. For example, occupational exposure may additionally relate to a more acute, accidental form of exposure that occurs in the context of one's occupation (e.g. occupational exposure of healthcare workers to a product). In contrast, accidental exposure is not defined in GVP or MTS:PTC and may refer to 'acute', sudden exposure in context of an accident which could also be the result of a medication error depending on the circumstances. In the wider context, occupational exposure is not normally considered to be associated with a medication error, although for pharmacovigilance purposes the majority of cases of occupational exposure would likely to be more of the acute/accidental type and therefore fall into the medication error category.

5.6.5. Off-label use versus medication error

In line with GVP VI.A.2.1.2 off-label use relates to situations where the medicinal product is *intentionally* used for a medical purpose not in accordance with the authorised product information. The focus is on the intention of the healthcare professional to use a product outside the authorised indication for other medical purposes. Medication error however refers to any *unintentional* error in the prescribing, dispensing, or administration of a medicinal product while in the control of a healthcare professional, a patient or a consumer. To determine when the use of medicine is outside of an authorised indication it is paramount to establish what are the authorised indications in a country or regulatory region, e.g. within the EU.

5.6.6. Overdose / underdose versus medication error and off-label use

Overdoses are not necessarily considered to be medication errors unless unintentional overdose occurred as a consequence of an error. In this situation it is important to code both concepts in order to facilitate case identification. Intentional overdose is not considered a medication error.

For the purposes of term selection and analysis of MedDRA-coded data, 'overdose' is more than the maximum recommended dose (in quantity and/or concentration), i.e., an excessive dose and underdose is the administration of less than the minimum recommended dose (in quantity and/or concentration).

Both over- and underdose may unintentionally be the result of a preceding medication error and relevant terms from either HLT *Overdose* or HLT *Maladministration* which currently includes the terms for underdose, may be chosen in combination with the associated medication error term.

5.6.7. Coding of medication errors with medical devices

For pharmacovigilance purposes device issues will be associated with drug delivery devices rather than medical devices although the MedDRA hierarchy contains a wide granularity of terms for those organisations/agencies/regions which also regulate medical devices.

There are separate concepts to consider when selecting device terms associated with medication error:

1. Device medication error terms falling into maladministration HLT in MedDRA hierarchy. These terms are most likely to be appropriate in pharmacovigilance for where a medication error has clearly occurred relating to a medicinal product delivery device.

2. Other terms in the device issues HLGT may relate to medication errors from device error/failure/quality issues or into user errors (e.g. device difficult to use). There are also some terms which are clearly medication errors (e.g. wrong device dispensed) which are uniaxial terms within the Device issues HLGT and not linked to medication error section of the hierarchy. For pharmacovigilance purposes the device will be a medicinal product delivery device and the consequence will be a medication error related to the drug. The example in the PTC TS shows a 'Wrong device used' (In device section of hierarchy only) and also recommends to code 'Accidental overdose' which falls into the medication error section of hierarchy.

Insulin was given using the wrong syringe resulting in the administration of an overdose. The patient developed hypoglycaemia.	Wrong device used Accidental overdose Hypoglycaemia	If an overdose is reported in the context of a medication error, the more specific term *LLT Accidental overdose* can be selected

The PT 'Device misuse' has subordinate LLTs which may be analogous to the concept of PT 'Intentional product misuse' which is recommended to be used for coding cases falling within the definition in section 1.3.8 but also may also be related to medication error, for example the LLT 'Device use beyond labelled duration' may be either intentional misuse or a medication error. The LLT 'Intentional device misuse' should only be used where there is information to confirm that it is intentional. Where no information is available if it is intentional or unintentional the LLTS without intention should be used (E.g. 'Inappropriate device therapy'. In circumstances where it is clear that it was an unintentional device use, LLTs should be selected subordinate to the PT 'Device use error'.

5.6.8. Standard MedDRA Query (SMQ) for medication errors

Following approval of the ICH advisory panel in September 2014 a SMQ for medication errors is currently being developed to support data retrieval, signal detection and assessment of medication errors in pharmacovigilance databases.

5.7. Rules of anonymisation of personal data

Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data provides the legal basis for the processing of personal data within the European Union. Regulation (EC) No 45/2001 regulates the protection of individuals with regard to

916 the processing of personal data by Community institutions and bodies, including the European
917 Medicines Agency.

918 The provisions of GVP VI.C.6.2.2.8 regarding the processing of personal data within the EudraVigilance
919 database for the purpose of safeguarding public health should also be applied to medication errors.

920 5.7.1. Anonymous reporting

921 Given the lack of EU harmonised legislation which protects healthcare professionals from potential
922 liability claims in relation to reporting medication errors for pharmacovigilance purposes, some EU
923 Member States have either implemented a no-blame policy or introduced anonymous reporting for
924 medication errors.

925 In accordance with the national laws of relevant EU Member States the potential liability may result
926 from claims that the classification of a suspected adverse reaction as a medication error made by the
927 marketing authorisation holder may be interpreted as implying that a third party (the healthcare
928 professional) has contributed to the occurrence of a medication error.

929 There is, therefore, a conflict between this potential liability and the implied pharmacovigilance
930 obligation of the marketing authorisation holder to classify medication errors as such when reporting
931 suspected adverse reactions to national competent authorities or the Agency. This conflict could be
932 potentially addressed by including a 'disclaimer' in the suspected adverse reaction report (ICSR)
933 submitted by the marketing authorisation holder to the national competent authority or the Agency:

934 *This suspected adverse reaction report is submitted and classified as a medication error solely and*
935 *exclusively to ensure the marketing authorisation holder's compliance with the requirements set out in*
936 *Directive 2001/83/EC and Module VI of the Good Pharmacovigilance Practices. The classification as a*
937 *medical error is in no way intended, nor should it be interpreted or construed as an allegation or claim*
938 *made by the marketing authorisation holder that any third party has contributed to or is to be held*
939 *liable for the occurrence of this medication error.*

940 The inclusion of this disclaimer may help minimise the potential exposure of the marketing
941 authorisation holder to claims that the classification of a suspected adverse reaction as a medication
942 error may be interpreted as implying that a third party has contributed to the occurrence of a
943 medication error.

944

6. Operation of the EU regulatory network

This chapter highlights the roles of key stakeholders involved in the collection, management and reporting of reports of medication errors regardless of whether associated with suspected adverse reactions.

The EU specific requirements, as defined in Directive 2001/83/EC, applicable to competent authorities in EU Member States and to marketing authorisation holders in relation to suspected adverse reactions associated with an error in the use of human medicinal products are explicitly highlighted.

The roles of consumers, healthcare professionals and patient safety organisations responsible for national patient safety incident reporting and learning systems in EU Member States in context of medication error reporting is also explained.

This chapter should be read in conjunction with the definitions and general principles detailed in chapter 1 and 2 of this guidance.

6.1. The role of competent authorities in EU Member States

The general provisions of GVP VI.C.2.1 regarding EU Member States' responsibilities for the collection and recording of reports of suspected adverse reactions apply.

Articles 107 and 107a of Directive 2001/83/EC impose a legal obligation on marketing authorisation holders and EU Member States to record and report suspected adverse reactions. For this purpose EU Member States operate a pharmacovigilance system to collect information on the risks of medicinal products with regard to patients' or public health, including suspected adverse reactions arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure [Directive 2001/83/EC, Article 101(1)]. This includes suspected adverse reactions arising from errors with human medicinal products.

EU Member States should also take all appropriate measures to encourage consumers (including patients) and healthcare professionals to report suspected adverse reactions, including those arising from medication errors, to the national competent authority (Directive 2001/83/EC, Article 102). For this purpose patient reporting should be facilitated through the provision of alternative reporting formats in addition to web-based formats which Competent Authorities provide on their national websites. National competent authorities should consider the recommendations[9] for minimum data elements to facilitate the implementation of web-based reporting forms to support consumer reporting of medication errors within their territory.

Furthermore, EU Member States have the obligation to evaluate the information received in the pharmacovigilance system scientifically, to detect any change to a medicine's risk-benefit balance, to consider options for risk minimisation and prevention and to take regulatory action concerning the marketing authorisation as necessary.

For this purpose competent authorities in EU Member States should systematically record and report medication errors associated with adverse reaction(s) which are brought to their attention in line with the ICSR general reporting requirements in GVP VI.B.7.

It is good practice that medication errors which do not fall in the definition of a reportable ICSR (i.e. intercepted errors, medication errors without harm and potential errors) which may be brought to the

[9] Reflection Paper on standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients (EMA/137945/2011)

competent authority's attention through exchange agreements with national patient safety organisations as outlined in chapter 6.2. are systematically recorded and the information taken into account e.g. for risk management activities as appropriate.

Complementary to the provisions of GVP module VI for the management and reporting of adverse reactions to medicinal products, EU Member States should promote the classification of medication errors proposed in chapter 4.3. to support the performance of their pharmacovigilance obligations, i.e. to evaluate medication error reports scientifically, to detect any change to a medicine's risk-benefit balance related to its erroneous use and to implement appropriate risk minimisation measures in a timely and efficient manner.

Accurate classification and coding of information pertinent to medication errors (see chapter 5.5.1.) will help to achieve the intended objectives of the pharmacovigilance legislation to strengthen the supervision of medicinal products and to enhance the protection of public health. The recommendation in GVP VI.C.6.2.3.3 to explicitly code medication errors in addition to the suspected adverse drug reaction(s) therefore reflects the intention of the EU legislator and the objectives of the revised pharmacovigilance legislation.

6.2. Collaboration with National patient safety organisations

The pharmacovigilance legislation includes provisions intended to stimulate co-operation between EU national pharmacovigilance centres and patient safety organisations (PSO) or any other authorities, bodies, organisations and/or institutions responsible for patient safety including patient safety incident reporting and learning systems established in Member States. The objective of this collaboration is to minimise preventable harm from medication errors by learning from failures of the healthcare system. The term 'patient safety incident' in this context refers to an event or circumstance which could have resulted, or did result, in unnecessary harm to a patient. The scope of this term encompasses the entire health care process whereas the scope of adverse reactions in pharmacovigilance refers to the use of medicines by a patient or healthcare professional. Patient safety incidents may occur in hospitals or other health care communities and may or may not involve a medicinal product. The harm to the patient may be caused by an error resulting in an adverse event or adverse reaction. Medication error incidents provide a valuable source of information regardless of whether or not the error is associated with adverse reaction(s). In some EU Member States there may be other mechanisms to collect data on medication error incidents outside of hospital settings, for example through poison control centres.

As explained in chapter 3. , Article 107a (5) of Directive 2001/83/EC requires EU Member States to ensure that adverse reaction reports arising from an error associated with the use of a medicinal product that are brought to their attention are *made available* to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that EU Member State. EU Member States shall also ensure that the authorities responsible for medicinal products within that EU Member State (i.e. NCA) are *informed* of any suspected adverse reactions brought to the attention of any other authority within that EU Member State.

Many but not all EU Member States have established patient safety organisations or national patient safety reporting and learning systems; therefore the implementation of these legal provisions is a national responsibility of the competent authority in each EU Member State and is limited to the exchange of information on medication error reports associated with suspected adverse drug reaction(s).

In EU Member States where a national system for reporting patient safety incidents exist, the national competent authority and the responsible patient safety organisation should work together to build efficient working relationships with the aim to improve the quality and extent of reporting of

medication errors and the resulting learning to maximize public health benefits of spontaneous reporting of medication errors. A formal exchange agreement between the two bodies should be signed to allow the exchange of information and of reports on medication errors. A good practice example for an exchange agreement is described in figure 6. It is acknowledged that individual EU Member States may use different models that best fit their national requirements.

The exchange agreement in figure 6 should cover medication error reports associated with adverse reaction(s) brought to the NCA's attention which should preferably be exchanged (*made available*) as individual reports with the PSO or any other authority in that EU Member State responsible for patient safety. In addition, it is good practice that PSOs provide the NCA with *information* about medication errors brought to their attention in a suitable format (e.g. summary tabulation, listings of individual cases etc.) regardless of whether the error is associated with adverse reaction(s). However, medication error reports associated with adverse reaction(s) should preferably be exchanged as individual reports to allow further processing in national pharmacovigilance databases and subsequent transmission to EudraVigilance by the competent authority.

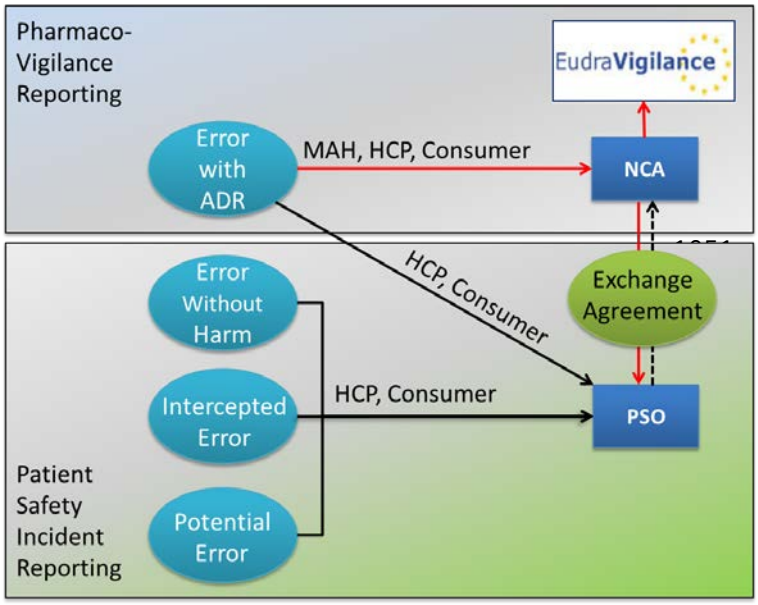


Figure 6: Model for collaboration between National Competent Authorities (NCA) and national patient safety organisations (PSO) for the exchange of medication errors. The red line between NCA and PSO refers to the legal provision to make medication error reports with ADR(s) *available*. The dotted line is a good practise recommendation to *inform* about medication errors regardless of whether associated with adverse drug reaction(s).

As part of the Monitoring Medicines project funded by the Research Directorate of the European Union under its Seventh Framework Programme, WHO has published a report[10] intended to stimulate cooperation between national pharmacovigilance centres and patient safety organisations to streamline collaborative efforts to minimise preventable harm from medicines. The report provides background and useful technical guidance on the principles and methods of medication error incident reporting and learning and provides a framework for the coordination and sharing of pharmacovigilance evidence.

6.3. The role of the Agency's Pharmacovigilance Risk Assessment Committee

In accordance with EU legislation the Agency coordinates the scientific resources and expertise put at its disposal by Member States for the performance of pharmacovigilance activities, in particular the pharmacovigilance tasks performed by the Pharmacovigilance and Risk Assessment Committee (PRAC). The PRAC is responsible for providing recommendations in relation to the detection, assessment,

[10] Reporting and learning systems for medication errors: the role of pharmacovigilance centres. World Health Organisation (2014)

minimisation and communication of risks of adverse reactions, including those arising from medication errors associated with the use of medicinal products authorised in the EU regardless of the route of authorisation (Article 61a(6) of Regulation (EC) 726/2004). During its monthly plenary meetings the PRAC evaluates and provides recommendations to the Committee for Human Medicinal Products (CHMP) or the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) for regulatory action on safety issues, including medication errors.

The PRAC performs the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance of a medicinal product, based on the evaluation of pharmacovigilance data reported to EudraVigilance.

In line with GVP module V.B.8.6.4 the RMP contains a dedicated section (Part II - SVI.4) which specifically elaborates on the potential for medication errors based on pre- and post-authorisation safety data reporting, including a review of preventive measures for the final product being marketed. The PRAC is also responsible for monitoring the outcome of risk minimisation measures and conditions of marketing authorisations for the safe and effective use of medicines which may be required to manage the risk of medication errors (Article 56(1)(aa) of Regulation (EC) 726/2004). This may include the design and evaluation of post-authorisation studies to further investigate medication errors in clinical practice. In this context the PRAC may provide recommendations to MAHs on protocols to study the utilisation of patterns of use of medicines under real life conditions with the objective to quantify the risk of medication errors and to measure the impact of regulatory interventions.

By analogy PSURs assessed by the PRAC include a dedicated section on aggregated data (summary reports) of medication errors that occurred during the reporting interval in chapter VII.B.5.9. This information is taken into consideration in the continuous evaluation of the benefits and risks of a medicinal product.

The specific pharmacovigilance tasks performed by the Agency are detailed in GVP module I.C.2.3 'Role of the European Medicines Agency' and corresponding GVP modules.

6.4. The role of healthcare professionals, patients and consumers

Regardless of legal obligations related to reporting requirements for pharmacovigilance purposes, consumers and healthcare professionals are critical stakeholders for successful learning from medication errors acting as primary source for reporting and providing first-hand information on the case. In accordance with the ICH E2D guideline a consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, or a friend, relative or carer of a patient. A healthcare professional is defined as a medically-qualified person such as a physician, a dentist, a pharmacist, a nurse, or as otherwise specified by local regulations.

Patient/consumer and healthcare professional reporting

The pharmacovigilance legislation promotes and facilitates adverse reaction reporting by patients, consumers and healthcare professionals through development and provision of standard web-based structured forms. In accordance with Articles 102 and 107(a) of Directive 2001/83/EC each EU Member State has the responsibility to record all suspected adverse reactions that occur in its territory which are brought to its attention by consumers and healthcare professionals, including follow-up of case reports, by means of national medicines web-portals or other means. To encourage reporting the legislation requires that all medicinal products include a standard text in the SmPC asking both healthcare professionals and patients to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a(1) of Directive 2001/83/EC. For this purpose the details (website URL and/or email address) of the national competent authorities' websites

are included in section 4.8 ‘Undesirable effects’ of the SmPC and section 4 ‘Possible side effects’ of the package leaflet accordingly.

Medicinal products which are subject to additional monitoring in accordance with Article 23 of Regulation (EC) 726/2004 include in addition a black triangle and a statement in both SmPC and package leaflet asking healthcare professionals and patients to report any suspected adverse reactions to allow quick identification of new safety information.

As described in GVP module VI.B.1.1.1 consumers and healthcare professionals may report medication errors as any other adverse reaction spontaneously to a competent authority, marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre) as unsolicited communication. Consumer reports should be documented and reported in accordance with GVP VI.

No blame reporting culture for healthcare professionals

Healthcare professionals should report errors of use of medicines which they either commit themselves or which they are made aware of through consumers, patients or any other third party regardless of whether the error is associated with suspected adverse reaction(s). As primary source of information healthcare professionals play a key role in providing relevant information on the parameters required for the scientific evaluation of the case (see chapter 5.5.1.) by marketing authorisation holders and regulatory authorities. The reporting of medication errors by healthcare professionals and consumers is in no way intended, nor should it be interpreted or construed by a marketing authorisation holder, national competent authority or any other third party as an admission, allegation or claim for potential liability, but for the sole purpose of the pharmacovigilance tasks as described in Title IX of Directive 2001/83/EC.

6.5. The role of marketing authorisation holders

MAHs are required to operate their own pharmacovigilance system for the fulfilment of pharmacovigilance tasks equivalent to the relevant EU Member State’s pharmacovigilance system. This includes the obligation to record, i.e. collect and collate all reports of suspected adverse reactions, including those arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure [Directive 2001/83/EC, Article 104].

MAHs are, therefore, legally required to report medication errors as part of their reporting obligation of suspected adverse reactions if the adverse reaction is associated with an error.

Directive 2001/83/EC does not explicitly require MAHs to classify suspected adverse reactions in different categories provided for in the definition of an adverse reaction (i.e. medication errors, overdose, occupational exposure, off-label use, use within the scope of the marketing authorisation, etc.). However, GVP Module VI.C.6.2.3.3 on ‘suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupational exposure’ contains a recommendation for MAHs to use the MedDRA Lowest Level Term (LLT) code to classify the medication error as such when reporting in EudraVigilance (see 2.5.1.).

For this purpose it is paramount that MAHs systematically record reports of medication errors which are brought to their attention but which do not fall in the definition of a reportable ICSR (i.e. intercepted errors, medication errors without harm and potential errors in line with chapter 4.3.2.) in their local pharmacovigilance database or equivalent system which allows for the collation of medication error reports both with and without associated adverse reaction(s) in the summary reports required for PSURs (see chapter 5.4.). This includes reports from literature, solicited reporting and

other sources. MAHs should make all reasonable efforts to follow-up the essential information referred to in table 2 (chapter 5.5.1.) for the analysis, scientific evaluation and interpretation of case reports of medication errors in line with the general provisions in chapter 5.5. and to include an analysis of this information in the summary report on medication errors provided for in GVP VII.B.5.9 in the PSUR.

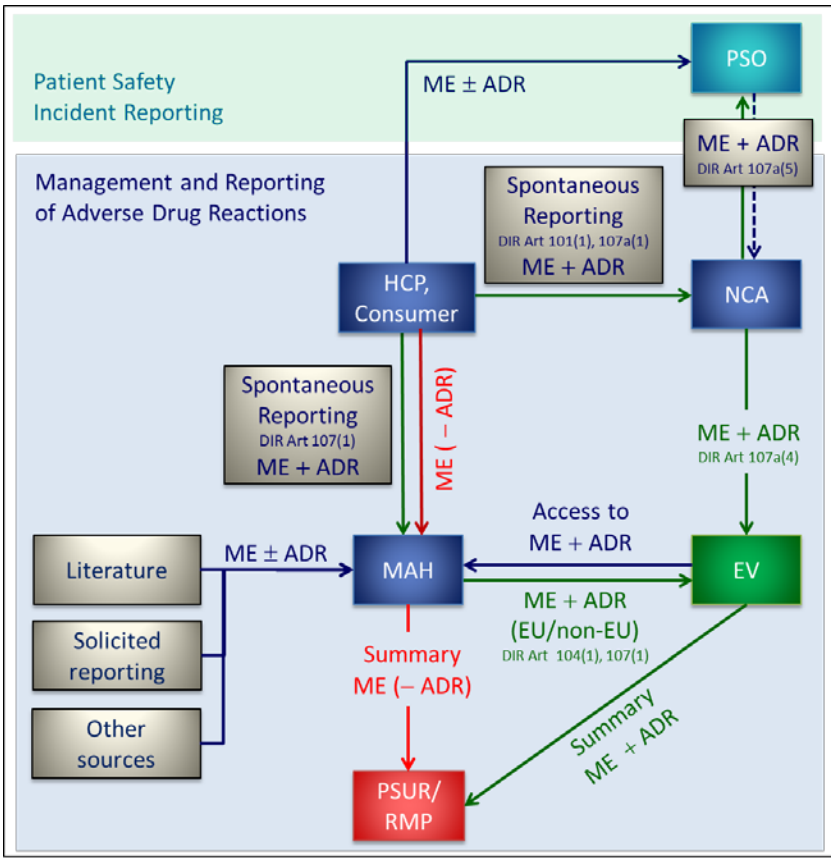
In addition, MAHs should provide additional listings of cases of medication errors not associated with ADRs upon request of a competent authority or the Agency to support the scientific evaluation and assessment of the summary reports provided in PSURs as outlined in chapter 5.4.

According to GVP V.B.8.6.4, the MAH should discuss in RMP module SVI medication errors which occurred both during the development phase and post-marketing, providing information on the errors, their potential cause(s) and possible remedies given but also taking into account potential reasons for medication errors. If adverse reactions occurred as a result of medication errors appropriate measures to minimise the risk of medication errors should be proposed. In this context, MAHs should also take into consideration the results of the analysis of the essential information referred to in table 2 (chapter 5.5.1.) as appropriate.

MAH should apply the classification of medication errors referred to in chapter 4.3.2. to facilitate these activities.

Annexes

Annex 1 - Simplified reporting rules for medication errors associated with adverse reactions post EudraVigilance audit



The graph shows the simplified information flow (green arrows) for medication errors reports associated with suspected adverse reactions (+ ADR) in line with EU reporting requirements of Directive 2001/83/EC after a successful EudraVigilance audit, and the stakeholders involved: marketing authorisation holders (MAH), national competent authorities (NCA) and authorities, bodies, organisations and/or institutions responsible for patient safety (PSO) where they exist within a Member State. The red arrows represent medication error reports not associated with suspected adverse reactions (– ADR) brought to the attention of MAHs and/or NCAs which are outside the scope of EU reporting requirements of Directive 2001/83/EC and should therefore not be submitted as ICSR, however such reports should be included as summary information in periodic safety updated reports (PSUR) and risk management plans (RMP) in line with GVP. From a public health perspective, it is good practise that NCAs in Member States are also informed of adverse reactions associated with medication errors which have been brought to the attention of a PSO in that Member State (dotted line).

Annex 2 - Template for summary tabulation and listing of individual cases of medication errors

In line with GVP VII.B.5.6 the PSUR includes interval and cumulative summary tabulations of adverse reactions including those associated with medication errors for the reporting interval. This annex provides a template for summary tabulations and for additional listings of individual cases of medication errors not included elsewhere in the PSUR, e.g. where medication errors are discussed as safety signal or safety concern.

The tables should be created automatically from the pharmacovigilance database but marketing authorisation holders may modify the tables to suit specific requirements, as appropriate.

For PSURs covering several medicinal products with the same active substance differences between indications, formulations and target populations may require separate tables (e.g. for medication errors with patches versus medication errors with oral formulation).

A summary tabulation as shown in table A2-1 should be included in GVP VII.C.5 as PSUR EU regional appendix, sub-section on medication errors with cross-references to GVP VII.B.5.9 MedDRA terminology should be applied for coding medication error related terms at MedDRA Preferred Term (PT) and Higher Level Term (HLT) levels based on spontaneous ICSRs in line with the provisions in chapter 5.6.

Table A2-1: Summary tabulation - numbers of Preferred Terms (PT) in the HLGT Medication Errors reported with serious or non-serious adverse reaction(s) from post-authorisation sources* for <invented name>.

HLGT Medication Errors[1]	**Spontaneous, including competent authorities (worldwide) and literature**					**Non-interventional post-marketing study and reports from other solicited sources ****	
	Serious		**Non-serious**		**Total Spontaneous**	**Serious**	
	Interval	**Cumulative**	**Interval**	**Cumulative**	**Cumulative**	**Interval**	**Cumulative**
<HLT 1>							
<PT>							
<PT>							
<HLT 2>							
<PT>							
<PT>							

[1] Consider MedDRA HLTs such as *Accidental exposures to Product*, *Maladministrations*, *Medication Errors NEC*, *Medication Monitoring Errors* and other relevant HLTs as applicable.

* Non-interventional post-authorisation studies, reports from other solicited sources and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, competent authorities (worldwide), and scientific literature)

** This does not include interventional clinical trials.

Additional listings of individual cases of medication errors of special interest shown in table A2-2 below may be provided upon request by the PRAC Rapporteur or a EU Member State through the Agency to support the assessment of medication errors in PSURs, particularly for medication errors of special interest or if constituting a safety concern in the risk management plan. Listings of individual cases as

shown in table A2-1 should be included in GVP VII.C.5 as PSUR EU regional appendix, sub-section on medication errors with cross-references to GVP VII.B.5.9 accordingly.

Table A2-2: Listings of individual cases of medication errors of special interest for <invented name>.

Medication error of special interest MedDRA Preferred Term(s)	Reported adverse reaction(s) MedDRA Preferred Term(s)	Medication stage (prescribing, dispensing, preparation, administration, monitoring)	Contributing factors (e.g. human behaviour, system related, transition of care, external beyond HCP / patient control)	Patient risk factors (e.g. paediatric, elderly, pregnancy, lactation, disease)	Ameliorating factors and corrective action(s)
<PT 1>					
<case 1>					
<case 2>					
<PT 2>					
<case 1>					
<case 2>					

Table A2-3: Listing of individual cases of medication error not associated with adverse reaction(s) from post-authorisation sources**** for <invented name>.

Type of error	Brief description	Medication stage (e.g. prescribing, dispensing, preparation, administration, monitoring)	Contributing factors (e.g. human behaviour, system related, transition of care, external beyond HCP / patient control)	Patient risk factors if patient involved	Mitigating factors preventing or moderating the progression of an error
Medication errors without harm					
<case 1>					
<case 2>					
Totals					
Intercepted errors					
<case 1>					
<case 2>					
Totals					
Potential errors					
<case 1>					
<case 2>					
Totals					

**** Reports from non-interventional post-authorisation studies and other solicited sources, reports from healthcare professionals and consumers and the scientific literature brought to the attention of the marketing authorisation holder

Annex 3 - Additional coding examples for medication errors complimentary to MTS:PTC documents

This Annex includes specific examples of medication errors in addition to those provided in the MTS:PTC documents to address. The MTS:PTC document in its latest version should always be consulted.

A. Medication errors reported with clinical consequences

If a medication error is reported with clinical consequences (with ADR/ADE), select terms for both the medication error and the clinical consequences.

Examples

Reported	LLT Term Selected	Comment
Patient experienced paraplegia after an epidural anaesthesia procedure was carried out with a needle contaminated with topical disinfectant	Accidental exposure to product; Exposure to contaminated device; Paraplegia;	This is a procedural error caused by the wrong use of the epidural needle as device.
Patent was inadvertently administered the higher strength of a calcium channel blocker and experienced hypotension	Incorrect dose administered; Hypotension;	Note the difference in concepts of dose, dosage and dosage form
Dose calculation error in an adolescent treated for growth failure results in insulin-like hypoglycaemia	Incorrect dose administered; Hypoglycaemia;	There is no term for coding dose calculation error but this information should be provided in the case narrative.
Patient was prescribed different insulin product at same daily dose and experienced hypoglycaemia	Wrong drug administered; Drug prescribing error; Hypoglycaemia;	
Patient was prescribed 10 fold higher strength of an oral opioid and went into respiratory failure at home after having taken 3 doses	Drug prescribing error; Respiratory failure; Accidental overdose	The PT Prescribed overdose should not be selected; the overdose is not intended and consequence of a medication error.
Patient well controlled on antiepileptic medicines failed to get repeat or emergency supply and was hospitalised with partial seizures	Drug dose omission; Partial seizures;	The fact that it is a supply issue cannot be coded and should be recorded in the narrative of the database.

B) Medication errors and potential medication errors reported without clinical consequences

Medication errors without clinical consequences are not adverse reactions, but as highlighted in chapter 5.4. they should also be recorded by MAHs if brought to their attention. Select a term that is closest to the description of medication error reported. Also the potential occurrence of a medication error and intercepted errors (or near misses) should be recorded and the term which is closest to the description of the error should be selected.

If specifically reported that no adverse effect has occurred, it is acceptable to select LLT No adverse effect.

In instances where the medication did not reach the patient, it is acceptable to select LLT Drug not taken in context of intercepted medication error.

Examples

Reported	LLT Term Selected	Comment
Patient was dispensed the wrong product due to confusion of packs. The product is available in two presentations, one colour coded and one not.	Product packaging confusion; Wrong drug dispensed;	The information that the product is available in 2 presentations with different colour code cannot be coded and should be provided in the case narrative.
Product preparation requires two pre-filled syringes to be mixed prior to administration in 15 steps to achieve homogenous solution for injection. This is a difficult procedure and will likely result in problems in preparation	Inappropriate preparation of medication Circumstance or information capable of leading to medication error;	This is an example for a potential medication error due the high number of preparation steps required.
Pharmacist reported confusion of product label of prolonged-release with immediate release formulation	Product Label confusion; Circumstance or information capable of leading to medication error;	This is an example of a potential medication error since the report does not state that the wrong product was actually dispensed. The most specific code for the reported potential medication error should be selected, and also the PT Circumstance or information capable of leading to medication error to capture that the error is a potential one.

C) Accidental exposure

Accidental exposure to medicines occurs if a medicinal product is used by someone other than the person the medicine was prescribed for, or if a person becomes inadvertently exposed. It may be harmful, and in some cases life-threatening. Adverse reactions following accidental exposure to a medicinal product associated with a medication error should always be reported. The principles for medication errors also apply to accidental exposures.

Example

Reported	LLT Term Selected	Comment
A child died after accidental exposure to a fentanyl patch which had fallen off another person without noticing and got stuck to the child.	Accidental exposure to product by child; Medicinal patch adhesion issue;	In this example the poor adhesion could also be a quality issue, however poor visibility of the patch may be one of several possible contributing factors;

D) Accidental overdose

A medication error may be associated with accidental overdose, however overdose per se is not considered a medication error. For the purposes of term selection and analysis of MedDRA-coded data, overdose is defined as more than the maximum recommended dose (in quantity and/or concentration), i.e. an excessive dose (see Appendix B, MedDRA Introductory Guide). If the report clearly states that the overdose is the result of a medication error the *PT Accidental overdose* should be used.

1267 Examples

Reported	LLT Term Selected	Comment
Patient was administered a 20% overdose due to a reconstitution error of a medicine where both the concentrate and the diluent vials contained an overfill not adequately communicated in the posology section of the SmPC	Inappropriate preparation of medication; Accidental overdose;	This is an example for a common reconstitution issue resulting in a preparation error and consequential accidental overdose.
Infant was administered overdose of antipyretic solution for infusion due to a confusion of 'mg' with 'ml'	Drug administration error; Accidental overdose;	The fact that the administration error occurred through a human error confusing mg with ml cannot be coded and should be reported in the case narrative.
Patient exposed to life-threatening overdose due to confusion of dilution requirements for generic (higher concentrated solution for infusion) with requirements for originator	Inappropriate dilution of medication; Accidental overdose;	

1268

1269

Annex 4 - Business process proposal for using ICH E2B (R3) for recording medication errors in ICSRs

This draft proposal for recording medication errors in ICSRs using ICH E2B (R3) was finalised by the EudraVigilance Expert Working Group (EWG) in March 2015 and should be read in connection with chapter 5.5.2. of this guidance.

Once implemented after a successful EudraVigilance audit, the ICH E2B (R3) data element G.k.10.r 'Additional information on drug (coded)' should always be populated with the respective code for medication error at drug level (i.e. code 7) if the primary source has indicated that any type of medication error may have occurred. As this is a repeatable field, other codes may be used as appropriate.

If there is no explicit indication of a medication error by the primary source which would clearly transpose into a MedDRA term in the reaction section but there is a hint that there may have occurred an error in the context of the clinical course description, the sender may choose to populate data element G.k.10.r at their discretion to 'flag' a medication error. The case should be followed up to confirm if there was actually a medication error. The use of G.k.10.r also refers to intercepted errors where the cases are recorded as ICSRs in the database for PSURs.

In addition to the flag, an appropriate MedDRA term should be selected in reaction (E.i.2.1b) or sender's diagnosis (H.3.r.1b) as applicable (see MedDRA Term Selection: Points to Consider).

The advantage of using the G.k.10.r flag is to identify medication error cases at drug level rather than only at case level.

The fields should be populated as follows:

Scenario	Flag G.k.10.r	Reaction E.i.2.1b	Sender's comment H.4	Sender's diagnosis H.3.r.1.b
Reported as medication error, sender agrees	✓	✓	As applicable	
Reported as medication error, sender assessment provides alternative 'diagnosis'	✓	✓	✓	✓
Not explicitly reported as medication error but information and assessment of case leads to suspicion that a medication error was involved	At discretion	MedDRA PTC: Do not infer	Disclaimer* may be used as an option	✓

*Disclaimer as referred to in chapter 5.7.1.