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

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Table of contents

Executive summary	5
1. Introduction	5
2. Scope	5
3. Legal basis	6
4. Definitions	7
4.1. Adverse event.....	8
4.2. Adverse reaction	8
4.3. Medication error	8
4.3.1. Medication errors and correlation with harm and preventability	9
4.3.2. Classification of medication error reports	9
4.3.3. Intercepted medication error ('near miss')	10
4.3.4. Potential medication error.....	10
4.4. Patient safety incident.....	11
4.5. Root cause analysis	11
5. Structure and processes	12
5.1. Recording of medication error reports	12
5.2. Coding medication error reports	14
5.2.1. Coding with Medical Dictionary for Regulatory Activities (MedDRA)	14
5.2.2. General coding principles and MedDRA term selection	15
5.2.3. Concept descriptions relevant for coding medication errors	15
5.2.4. Medicinal product unavailability versus medication error	16
5.2.5. Accidental and occupational exposures versus medication error.....	17
5.2.6. Off-label use versus medication error and misuse	17
5.2.7. Overdose/underdose versus medication error.....	17
5.2.8. Product quality issues versus medication errors	18
5.2.9. Coding of medication errors in context of drug delivery devices	18
5.2.10. Standardised MedDRA Query for medication errors	18
5.3. Reporting requirements for medication errors associated with adverse reactions	19
5.3.1. Medication errors related to (invented) names	21
5.3.2. Medication error reporting as emerging safety issue.....	21
5.4. Periodic reporting of medication errors without adverse reaction(s)	21
5.5. Follow-up of medication error reports	23
5.5.1. Parameters to follow up when reporting medication errors	23
5.5.2. ICH E2B (R3) 'Additional information on drug' data element.....	28
5.6. Rules of anonymisation of personal data	28
5.6.1. Healthcare professional reporting	29

5.6.2. Potential liability aspects	29
6. Operation of the EU regulatory network	30
6.1. The role of competent authorities in EU Member States.....	30
6.1.1. Collaboration with national patient safety organisations.....	30
6.2. The role of the Agency’s Pharmacovigilance Risk Assessment Committee	32
6.3. The role of healthcare professionals, patients and consumers	32
6.4. The role of marketing authorisation holders	33
List of acronyms	34
Annexes	35
Annex 1 - Simplified reporting rules for medication errors associated with adverse reactions post EudraVigilance audit.....	35
Annex 2 - Templates for summary tabulation and listing of individual cases of medication errors.....	36
Annex 3 - Additional coding examples for medication errors.....	38
Annex 4 - Business process proposal for using ICH E2B (R3) for recording medication errors in ICSRs	42

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) was mandated to develop in collaboration with the EU regulatory network specific guidance for medication errors, taking into account the recommendations of a stakeholder workshop held in London in 2013.

This good practice guide is a key deliverable of the EU regulatory network's medication error initiative to improve reporting and learning from medication errors for the benefit of public health.

1. Introduction

Errors associated with the use of medicinal products are a major public-health burden and may happen when patients receive healthcare services for preventive, diagnostic, curative or rehabilitative purposes. It has been estimated that 18.7 - 56% of all adverse events that occur among hospitalised patients result from medication errors that would be preventable. Medication errors are thus a concern at all stages of health care delivery in European health care systems¹.

Medication errors occur as unintended mistakes in the process of prescribing, storing, dispensing, preparing or administering medicinal products in clinical practice. If a medication error occurs with the same pattern or at an unacceptable frequency, or if it results in serious harm for the patient, it is essential to understand the causes, contributing factors and clinical consequences of the error, as well as possible mitigating actions and solutions which could prevent the error from happening again.

2. Scope

The scope of this good practice guide includes the recording, coding, reporting and assessment of medication errors with medicinal products associated with suspected adverse reaction(s) in everyday medical practice. This guide is therefore relevant to 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 prescribing, storing, dispensing, preparing for administration or administering a medicinal product for human use authorised in the EU, regardless of the route of authorisation or the legal status of the medicinal product.

The recording, coding, reporting and assessment of events associated with intentional overdose, abuse, misuse, occupational exposure, off-label use and of medication errors occurring in the context of clinical trials conducted in accordance with Regulation (EU) No 536/2014, repealing Directive 2001/20/EC, are 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

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.

evaluation of medicinal products. This guide therefore also provides recommendations for marketing authorisation holders for recording, coding, reporting and assessment of medication errors brought to their attention (e.g. through direct patient or healthcare professional reporting) which are not associated with adverse reaction(s).

The scope of this guide also includes coding of medication error reports based on the Medical Dictionary for Regulatory Activities (MedDRA) term selection recommendations in the context of EU pharmacovigilance obligations. Specific coding examples are provided in addition to the guidance of the MedDRA Term Selection Points to Consider (MTS:PTC) document.

The guidance acknowledges the fundamental role of patient safety incident reporting systems (see chapter 4.4.) established in several EU Member States 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, the authorities, bodies, organisations and/or institutions responsible for patient safety incident reporting in EU Member States are outside the remit 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 incident reporting and learning systems in EU Member States. A model of collaboration and exchange of information is introduced as an example for good practice. It acknowledges 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.

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. This includes suspected adverse reactions arising from errors with human medicinal products.

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 national patient safety organisations (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 PSO to tackle medication errors by introducing appropriate changes to clinical practice, which is outside the legal remit of competent authorities in EU Member States. From a regulatory perspective learning from medication incident reports associated with adverse reactions will strengthen the monitoring of the safety of authorised medicinal products.

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 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 risk management plan which describes the risk management system for the concerned product.

The European Commission Implementing Regulation (EU) No 520/2012 provides the format and content requirements for PSUR and RMP. Article 34 (1) requires that the PSUR shall be based on all available data which provides the legal basis for summary information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes in line with GVP Module VII (Rev 1).

The reporting of medication errors occurring in the context of clinical trials is outside the scope of this guidance and will be addressed in the context of the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC, which 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). Annex III of Regulation (EU) No 536/2014 on safety reporting 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 and GVP Annex 1 (Rev 3) should be applied for the purpose of this guidance; of particular relevance for recording, coding, 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 ICH E2D guidelines² and WHO guidance³.

This guidance should be read in conjunction with the following EU and international guidance in its latest version, including the provided definitions:

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)

- GVP Module V on risk management systems
- GVP Module VI on the management and reporting of adverse reactions to medicinal products
- GVP Module VII 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 content of which is consistent with GVP Module VII on periodic safety update report
- ICH-Endorsed Guide for MedDRA Users: MedDRA® Term Selection (MTS) and MedDRA® Data Retrieval and Presentation (DRP): Points to Consider (PTC) documents

4.1. Adverse event

GVP Annex I (Rev 3) defines an adverse event as 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 guidance medication related adverse events should be distinguished from other adverse events (e.g. fall, surgery on wrong body site etc.).

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 this guidance and building on the GVP VI principles the following 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.

A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures.

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 pharmacovigilance reporting requirements for medication errors associated with adverse reactions 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 (i.e. associated with adverse reaction(s)) and preventability. An adverse reaction that results from an error in the medication use process is considered preventable, in contrast to a generally non-preventable adverse reaction which is labelled e.g. in SmPC section 4.8 as an undesirable effect of a medicine, i.e. for which the probability of harm to the patient is known and accepted and will likely occur depending on the frequency of the adverse reaction and on other circumstances such as co-medication. There are also medication errors which do not necessarily result in harm (i.e. there is no associated adverse reaction) but which may have other unwanted effects e.g. from an economic or environmental point of view. If an error occurred but was recognised and intercepted before reaching the patient, a potential adverse reaction was prevented and this is referred to as intercepted error.

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

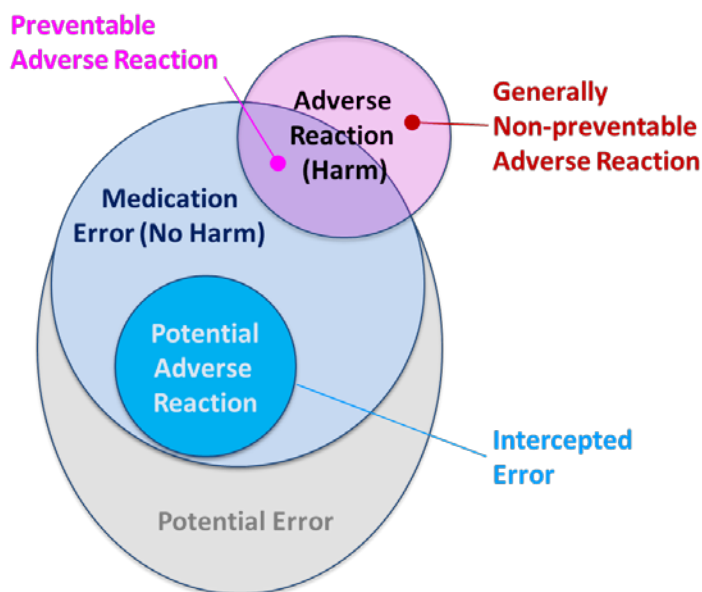


Figure 1: Correlation between medication errors, preventable and generally non-preventable adverse reactions and intercepted errors (modified according to Morimoto et al., Qual Saf Health Care 2004; 13: 306-314). The diagram is intended to explain, for illustrative purposes only, the concept of medication 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 guidance and to facilitate recording, coding, reporting and assessment medication errors should be classified based on factual information on the case. 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 depending on where the break occurs in the chain of events leading to the error and its consequences for the patient, 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.

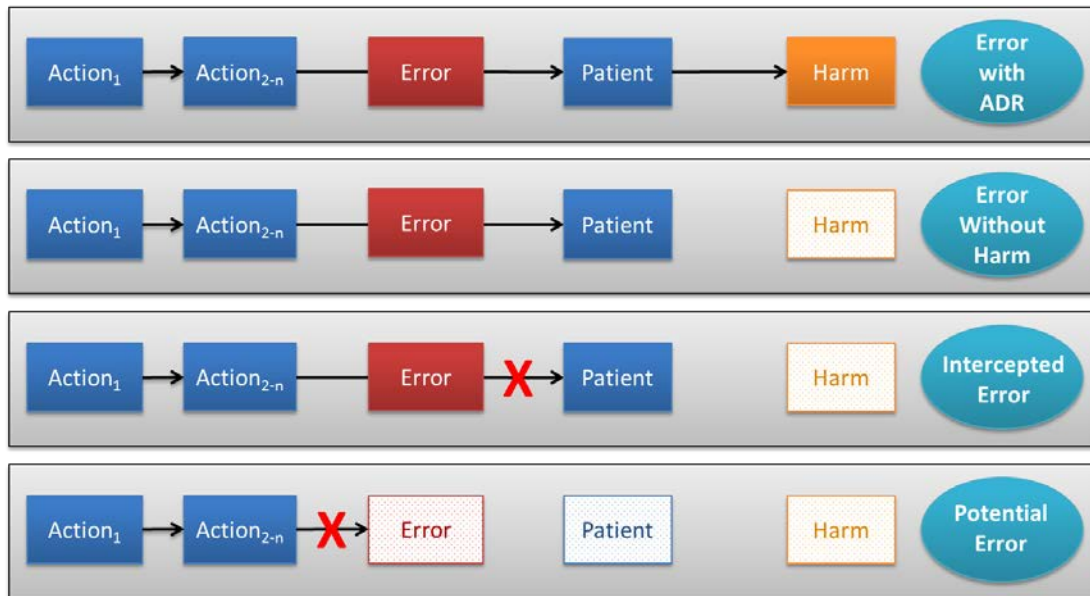


Figure 2: Concept for the classification of medication error reports for pharmacovigilance purposes. Depending on the break in the chain of events (represented by X), medication errors may be classified as error with ADR, error without harm, intercepted error and potential error.

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 in the treatment process before reaching the patient which would have resulted in a 'potential' ADR. The intervention has prevented actual harm being caused to the patient, e.g. a wrongly prepared medicine was actually not administered to the patient because the error was noticed by the nurse.

In the context of patient safety reporting systems the term 'near miss' is used as synonym for describing what is classified '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 for harm 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 all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process and may lead to

- a) a medication error with harm, but without knowing the actual cause,
- b) a medication error without harm and without knowing the actual cause, or
- c) a medication error without harm, but with the awareness of the actual cause.

Following this approach, errors could be assigned to at least one of the above scenarios a, b or c with blurred borders between these scenarios. For example, the indication of the strength of the active

substance in oral solutions may vary amongst different marketing authorisation holders with some labels referring to 'mg/ml' and others to 'mg/dose'. Before switching medications it is therefore necessary to perform a dose calculation to ensure that the applied dose remains unchanged. Otherwise, a patient could be exposed to accidental overdose due to misinterpretation of the concentration and the actual amount of active substance per dose. Applying the above scenarios this might have led to a medication error with or without harm in accordance with a) or b).

In another example a pharmacist noticed that the names of two medicines are similar and could clearly lead to product name confusion in practice, but no patient was actually involved or has taking the medicine. This potential medication error could be assigned to above scenario c). Since no patient was involved consequently no harm occurred, but the potential for error exists and such cases should be included in the relevant PSUR sections to allow regulators to take action to minimise the risk. In this example of a product name confusion 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. Patient safety incident

WHO's Conceptual Framework for International Classification for Patient Safety (WHO ICPS) defines a patient safety incident as an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient.

The scope of patient safety incidents covers the entire health care process whereas the scope of (suspected) adverse reactions in pharmacovigilance is limited to the use of medicines by a consumer or healthcare professional. Patient safety incidents may occur in hospitals or other health care communities and may or may not involve a medicinal product.

4.5. Root cause analysis

WHO's Conceptual Framework for International Classification for Patient Safety (WHO 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 some medication errors root cause analysis may not be the most appropriate method and alternatively a system analysis or patient safety analysis may be considered.

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.

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 applied. EU requirements are presented in chapter 6.

5.1. Recording of medication error reports

Medication errors associated with the use of a medicinal product may be reported spontaneously as unsolicited communication by a healthcare professional or a consumer to a competent authority, a marketing authorisation holder or another organisation (e.g. regional pharmacovigilance centre, poison control centre, PSO etc.) or may be reported in the context of solicited reports of suspected adverse reactions derived from organised data collection systems such as non-interventional studies or registries. Medication errors may also be identified from literature reports or other non-medical sources in line with GVP VI.B.1.1.

Suspected (serious and non-serious) adverse reactions associated with medication errors, i.e. where the suspected adverse reaction is a direct response to the medicinal product and was caused by an error, should be recorded, reported and assessed. The legal requirements 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 record medication errors associated with adverse reaction(s) as ICSR in ICH E2B format in the local (MAH) or national (NCAs) pharmacovigilance database respectively.

GVP VI.B.2 provides that reports, for which the minimum information for a valid ICSR remains incomplete after appropriate follow-up (see chapter 5.5.), should nevertheless be recorded in the pharmacovigilance system to support on-going safety or benefit-risk evaluation activities. This provision also applies to medication errors not associated with adverse reaction(s) referred to in chapter 4.3.2.

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 are not reportable as valid ICSR in accordance with GVP VI (see chapter 5.3.). Marketing authorisation holders may use alternative formats for recording those medication errors as appropriate (e.g. stakeholder database using other than ICH E2B standards) or if required by national legislation.

From a national 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 unintended or unexpected patient safety incidents 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. Some EU Member States have established regional and/or national patient safety organisations (PSO) which collect and analyse patient safety incident reports (see chapter 4.4. for definition) to improve patient safety in local/regional healthcare systems.

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 chapter 6.1.1.). In line with the proposed exchange agreement between NCA and PSO 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. It is good practice that NCAs also systematically record information about medication errors not associated with adverse reaction(s) which may be brought to their attention through such agreement.

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 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 6.4.), applying the classification described in chapter 4.3.2. of this guidance. Based on this classification, table 1 provides an overview how medication errors are recorded for pharmacovigilance purposes and from a patient safety perspective. In addition, table 1 shows the reporting requirements for marketing authorisation holders in line with EU pharmacovigilance obligations and relevant GVP recommendations.

Table 1: Recording medication errors.

			Patient Safety	Pharmacovigilance	
Medication Error Type	Error Occurred	Harm (ADR)	Recording	Recording	Report Type/ Relevance
Error with ADR	✓	✓	Incident with harm	Medication error with adverse reaction(s)	ICSR reportable to NCA and/or EV ³ ; PSUR summary ¹ ; RMP;
Error Without Harm	✓	✗	Incident	Medication error without adverse reaction(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	MTS:PTC guidance: PT '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 WHO ICPS definition of a patient safety incident which is an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient. 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 claimed that it has been prevented.

³ For ICSR reporting modalities please refer to GVP VI.C.4.1 for interim arrangements and GVP VI.C.4.2 for final arrangements applicable after successful EudraVigilance audit (see also chapter 5.3. and Annex 1).

5.2. Coding medication error reports

The terminology stakeholders may use for coding medication error reports will depend on the purpose. Marketing authorisation holders and national competent authorities complying with EU pharmacovigilance reporting requirements in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 will use the Medical Dictionary for Regulatory Activities (MedDRA)⁴ which is the terminology used worldwide by regulatory authorities, pharmaceutical companies, clinical research organisations and affiliated health care professionals for sharing information on 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, benefit-risk 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.

Healthcare professionals, patients and consumers are not required to use MedDRA when reporting adverse reactions spontaneously.

There is currently no commonly agreed terminology used for recording patient safety incident reports as referred to in chapter 4.4. in national reporting and learning systems of EU Member States where they exist in accordance with national legislation. The World Health Organization (WHO) has examined national patient safety incident reporting and learning systems and a major milestone was the launch of the WHO Conceptual Framework for the International Classification for Patient Safety (WHO ICPS) as a basis for a common language. 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](#).

5.2.1. Coding with Medical Dictionary for Regulatory Activities (MedDRA)

The MedDRA terminology allows for coding the stage of the drug treatment process where the error occurred, the circumstances and the (potential) clinical consequences regardless of whether the medication error is associated with adverse reaction(s).

The latest version of the ICH-endorsed guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' (MTS:PTC) document provides comprehensive guidance including examples of how MedDRA terms are assigned to verbatim reports of medication errors and related information on the type of error, the causes (i.e. contributing factors related to human behaviour), clinical consequences (i.e. adverse reactions), symptoms and diseases. MTS:PTC should always be consulted in conjunction with this guidance for accurate and consistent term selection. The MedDRA Introductory Guide provides concept descriptions for interpretation and coding purposes.

MTS:PTC and the MedDRA Introductory Guide are available for download from the MedDRA website (www.meddra.org).

⁴ MedDRA®, the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by IFPMA on behalf of ICH."

5.2.2. General coding principles and MedDRA term selection

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 provides that if a case of medication error is reported with clinical consequences, the MedDRA Lowest Level Term (LLT), corresponding to the term closest to the description of the reported medication error should be added to the term for the suspected adverse reaction in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' [ICH E2B (R2) B.2.i.1 or ICH E2B (R3) E.i.2.1], in line with the recommendations of MTS:PTC.

It is recommended to use the MedDRA browser to identify available terms. The current (or previous) version of MedDRA should be used and corresponding changes to the MedDRA term hierarchy taken into account. Within the *SOC Injury, poisoning and procedural complications* the *HLGT Medication errors* provides terms which are most relevant for coding medication errors.

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 the information provided by the primary source clearly describes a medication error. This principle equally applies to cases of 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)'.

Annex 3 provides additional coding examples with relevance for EU pharmacovigilance reporting requirements.

5.2.3. Concept descriptions relevant for coding medication errors

This chapter provides considerations on concepts relevant for coding and interpretation of medication errors in context of EU pharmacovigilance reporting requirements. These considerations may not entirely reflect current coding practices agreed across all ICH regions.

5.2.3.1. Coding different stages of a medication error

Medication errors may trigger a series of events as shown in figure 2 and there may be more than one stage in the drug treatment process affected by an error, e.g. a prescription error, if not intercepted, would lead to a dispensing error and consequently result in an administration error.

For coding purposes it is most important to capture the primary stage of the medication process where the error first occurred (e.g. prescribing error) and any subsequent error reaching the patient (e.g. administration error), including the clinical consequences for the patient.

5.2.3.2. Intercepted and potential errors

The concept of intercepted errors referred to in chapter 4.3.3. is also reflected in MedDRA providing several terms (e.g. *PT Intercepted medication error*) for coding and data retrieval purposes. Also potential medication errors as referred to in chapter 4.3.4. can be captured with MedDRA, e.g. through the *PT Circumstance or information capable of leading to medication error*.

5.2.3.3. Medication error in context of a contraindication

A medicinal product may be prescribed and administered to a patient in whom it is contraindicated, because the prescriber or caregiver is unaware that there is a contraindication labelled in the SmPC. This should be coded with the *LLT Contraindicated drug administered*. Where a medicinal product is

prescribed and administered to a patient in whom it is contraindicated, because the prescriber or caregiver is unaware that the patient has a disease that causes the drug to be contraindicated, the *LLT Labelled drug disease interaction medication error* should be coded in line with MTS:PTC. If the prescriber knows that a medicinal product is contraindicated, but intentionally prescribes it anyway this is considered off-label use and should be coded accordingly.

5.2.3.4. Treatment non-compliance of the patient

Patient non-compliance with a prescribed treatment or course of medication may result from a variety of factors and a common scenario is *intentional* non-compliance if the patient decides not to take the prescribed medicine (e.g. antibiotic course not completed) because the patient feels better.

If there is an element of intention implied, similar to the concept of intentional overdose/underdose and off-label use described in chapter 5.2.7., this would not be considered 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.

5.2.3.5. 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 (re-challenge) 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.

5.2.3.6. Ambiguous information

A report can only be best coded according to the information available. If the information is limited or ambiguous, attempts to follow up to ascertain missing or conflicting information should be made in line with GVP VI.B.3. If it is not possible to establish whether the event occurred due to an intentional decision made by the healthcare professional, patient or consumer, or whether it occurred unintentionally, it may be appropriate to use a more general MedDRA term from the *HLT Product use issues NEC*.

5.2.3.7. Lack of efficacy

Lack of efficacy of a medicinal product is not considered a medication error per se. There may be medication errors which lead to a lack of efficacy in the patient, for example where a patient has accidentally received an underdose. The coding should reflect the error and include e.g. the *PT Drug ineffective*.

5.2.4. Medicinal product unavailability versus medication error

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 applicable⁵. A product availability issue could be coded with *LLT Drug supply chain interruption* (MedDRA version 18.0).

5.2.5. 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 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. Occupational exposure in the wider context is generally not considered a medication error, however for pharmacovigilance purposes if the exposure happened suddenly and accidentally it may well be considered an error which should be coded with appropriate MedDRA terms to reflect both the medication error and the occupational exposure.

5.2.6. Off-label use versus medication error and misuse

Medication errors should be clearly distinguished from off-label use. 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 conditions of use. Medication error however refers to any *unintended* failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. To determine when a medicine is used outside the authorised conditions it is paramount to establish what are the authorised conditions in a country or regulatory region, e.g. within the EU.

Medication errors should be clearly distinguished from misuse. In line with GVP VI.A.2.1.2 misuse relates to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. The focus is on the intention of the patient or consumer to use a product outside the authorised conditions. For cases where a patient has misunderstood the instructions for how to use the medicine correctly, this should be considered an error and appropriate MedDRA terms selected to represent the event, e.g. *LLT Tablet crushed incorrectly*.

5.2.7. Overdose/underdose versus medication error

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 means more than the maximum recommended dose (in quantity and/or concentration), i.e. an excessive dose, whereas underdose is the administration of less than the minimum recommended dose (in quantity and/or concentration).

⁵ 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=WCOB01ac0580745911

Both over- and underdose may unintentionally be the result of a preceding medication error and relevant terms from the *HLT Maladministrations* may be chosen in combination with the associated medication error term.

5.2.8. Product quality issues versus medication errors

Product quality issues are abnormalities that may be introduced during the manufacturing, labelling, packaging, shipping, handling or storing process of a medicinal product. They should be distinguished and carefully evaluated if they fall in the definition of a medication error provided in chapter 4.3. For example, an underdose of antibiotic was administered because the lines on the dropper were hard to read which led to a medication error (accidental underdose).

5.2.9. Coding of medication errors in context of drug delivery devices

The reporting of errors involving medical devices authorised in accordance with Directive 93/42/EEC is in the remit of EU Member States' national legislation and outside the scope of this guidance.

For EU pharmacovigilance purposes appropriate coding of medication errors associated with drug delivery devices (e.g. errors with pre-filled insulin injector devices which are relatively common in everyday medical practice), is paramount. Medication errors involving a drug delivery device may be related to wrong use of the device with clinical consequence for the patient related to the drug.

The *HLT Maladministrations* contains terms for errors associated with drug delivery devices. Other terms in the *HLGT Device issues* may be relevant as appropriate.

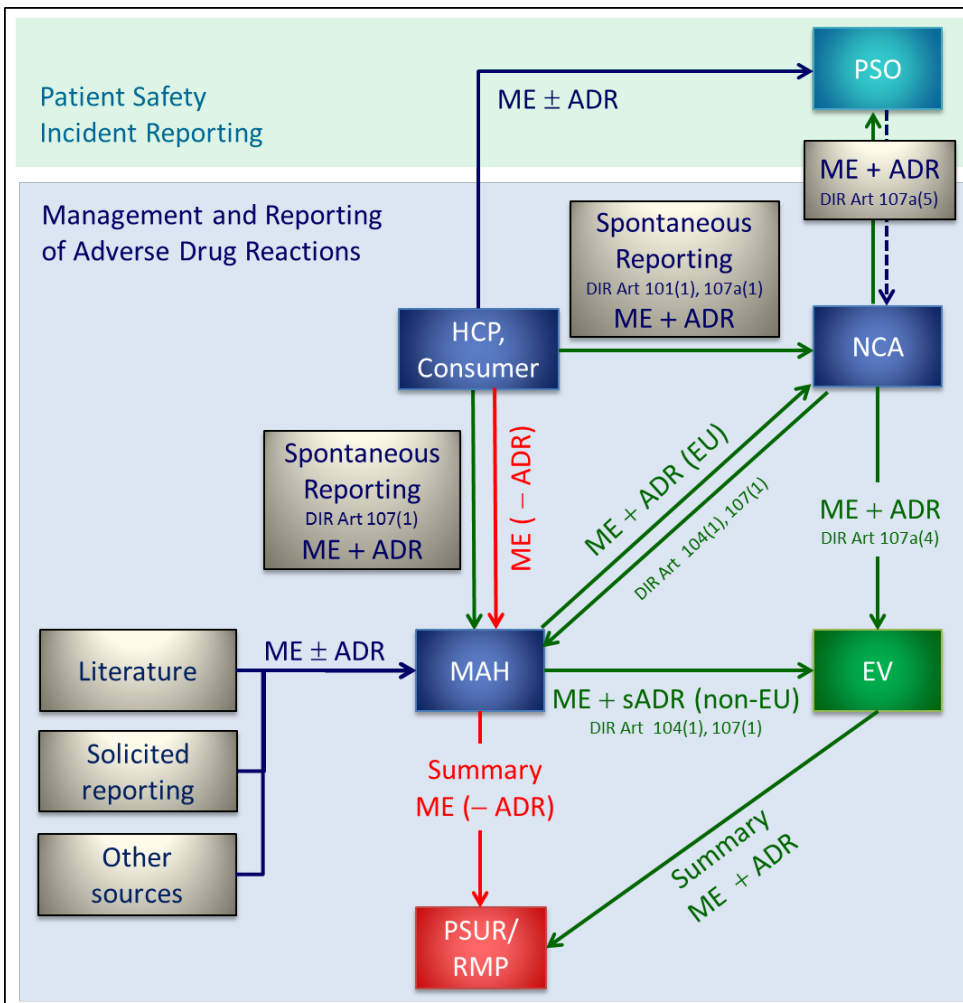
5.2.10. Standardised MedDRA Query for medication errors

Following approval of the ICH advisory panel in September 2014 a Standardised MedDRA Query (SMQ) for medication errors is currently being developed to support data retrieval, signal detection and assessment of medication errors in pharmacovigilance databases. The use of this SMQ is recommended as it becomes available.

5.3. Reporting requirements for medication errors associated with adverse reactions

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 including observational studies, registries etc. with the exception of clinical trials⁶ which are outside the scope of this guidance. 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 and Regulation (EC) No 726/2004 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 takes into account the role of national patient safety organisations as referred to in Article 107a (5) of Directive 2001/83/EC.



⁶ Medication error reporting in context of 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, repealing Directive 2001/20/EC, is outside the scope of this guidance and will be addressed elsewhere.

Figure 3: The diagram shows the information flow (blue arrows) of medication errors reports and the stakeholders involved: marketing authorisation holders (MAH), national competent authorities (NCA), healthcare professionals and consumers, 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 green arrows represent medication errors reports associated with suspected (serious and non-serious) adverse reaction(s) (+ ADR) or suspected serious adverse reaction(s) only (+ sADR) in line with EU reporting requirements 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 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 practice 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 (blue dotted arrow).

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.

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 States as ICSR in line with the 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 provisions of GVP VI Appendix 3 apply.

In line with the provisions of GVP Module VII.B.5 the PSUR includes cumulative summary tabulations of serious adverse events from clinical trials and cumulative and interval summary tabulations of adverse reactions from post-marketing data sources. These summary tabulations are created from the MAHs' pharmacovigilance system and include all the cases received by the MAHs, including those accessible from EudraVigilance, taking into account the need for data reconciliation by means of the worldwide unique case identifier. The data and assessments in the PSUR in relation to medication errors should include spontaneous (serious and non-serious) ISCRs associated with medication errors as well as clinical trials, non-interventional studies and other non-interventional solicited sources. When a medication error becomes a safety signal or a safety concern in the risk management plan, this should be evaluated in the relevant PSUR sections. 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'. For data retrieval purposes the Standardised MedDRA Query (SMQ) for medication errors referred to in chapter 5.2.10. should be considered.

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 obligations⁷ (see Annex 1), reports on medication errors will be made available in the EudraVigilance data analysis system (EVDAS) in line with the revised EudraVigilance access policy published on the Agency's website.

In line with the provisions of GVP VII.C.4.2.2, in exceptional circumstances the assessment of the causes and circumstances that led to a medication error may be supported by additional listings of

⁷ Article 24(2) of Regulation (EC) No 726/2004.

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 described in chapter 5.2.1. should be applied. Any such requests should be duly justified by the competent authority or the Agency and proportionate to the risk associated with the medication error.

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

5.3.1. Medication errors related to (invented) names

The checking of invented or generic trade names, referred to as (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 by marketing authorisation holders or applicants 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 reporting an (invented) name confusion as ICSR, the names of both medicinal products involved in the confusion should be provided in the drug section regardless of 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.

5.3.2. Medication error reporting as emerging safety issue

If a medication error constitutes an important safety concern which impacts on the overall benefit-risk balance of the medicinal product involved or on public health, such case should be notified by the marketing authorisation holder in line with the provisions 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.

5.4. Periodic reporting of medication errors without adverse reaction(s)

Medication errors without suspected adverse reaction do not fall in the definition of a valid reportable ICSR in line with GVP VI.B.2.

By analogy, intercepted errors (see definition 4.3.3.) and potential errors (see definition 4.3.4.) occurring in the context of the use of medicinal products are not reportable as ICSR to competent authorities responsible for medicinal products or to EudraVigilance.

Medication errors without suspected adverse drug reaction brought to the attention of marketing authorisation holders 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 be systematically recorded and assessed 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' taking into account reports from 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.

Medication errors not associated with adverse reaction(s) may be included in the additional listings of individual cases of medication errors of special interest referred to in chapter 5.3. and Annex 2 to support the assessment of causes and circumstances.

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



Figure 4: GVP requires MAHs to summarise information on patterns of medication errors in PSUR and RMP regardless of whether associated with adverse reaction(s).

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 4. The following information should be provided based on the summary tabulations or additional listings of individual cases provided in the PSUR (see Annex 2):

- Description of error (based on classification described in chapter 4.3.2.)
- 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. The good practice guide on risk minimisation and prevention of medication errors⁸ provides further details.

⁸ Good practice guide on risk minimisation and prevention of medication errors (EMA/606103/2014).

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 in accordance with GVP VI.B.2.

Specifically, GVP Module VI.B.6.3 provides that reports of medication errors associated with suspected adverse reaction(s) should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes and context of occurrence. Follow-up is particularly relevant 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.

To ensure better learning from any failures in the drug treatment process, it is good practice that marketing authorisation holders and national competent authorities make all reasonable efforts⁹ to collect, through appropriate case follow-up, comprehensive information in relation to any medication error brought to their attention regardless of whether the error was associated with adverse reaction(s), unless national requirements for anonymous reporting prevent follow-up.

5.5.1. Parameters to follow up when reporting medication errors

Table 2 provides an overview of parameters which constitute comprehensive information for medication error reports contributing to the scientific evaluation of the case regardless of whether the error was associated with adverse reaction(s). These parameters should also be considered in pre-populated questionnaires in local language for easy follow-up with the primary source in accordance with GVP VI.B.3. For medication errors reportable as ICSR, the table provides the respective ICH E2B ICSR data elements where the comprehensive follow-up information should be populated.

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 4.5.) 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 in RMPs intended to prevent or reduce the occurrence of medication errors. 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).

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

- Classification 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 for harm if a potential error or intercepted error did actually happen and reach the patient or consumer

⁹ Reasonable efforts in this context take into account national requirements for patient and reporter confidentiality and proportionate follow-up activities to avoid future spontaneous reporting is discouraged.

- Medicinal product(s) involved
- Batch number if the error is due to device failure

Table 2: Parameters to follow up when reporting medication errors

Parameter	Description	ICSR Data element ICH E2B (R2)	ICSR Data element ICH E2B R(3)
Setting	<p>Inpatient (hospital, nursing home, care home), outpatient (general practitioner, specialist practice, ambulatory), pharmacy, drug store, private home, etc.</p> <p>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 5.6.2.</p>	<p>A.2 Primary source</p> <p>B.5 Narrative (Narrative information should only provide general setting not reporter information)</p>	<p>C.2.r Primary source</p> <p>H.1 Narrative</p> <p>H.5 Case narrative in native language (Narrative information should only provide general setting not reporter information)</p>
Stage of medication process	<p>The appropriate MedDRA LLT (either single term or combination of terms) should be reported in the reaction field and described in the narrative as applicable. If not initially clear from verbatim information, the stage of the medication process where the error occurred should be ascertained:</p> <ul style="list-style-type: none"> • Prescribing • Storage in clinical practice • Dispensing • Preparation for administration • Administration 	<p>B.2.i.1.b Reaction/ event in MedDRA terminology</p> <p>B.5.3.b Sender's diagnosis</p> <p>B.5 Narrative</p>	<p>E.i.2.1 Reaction/event</p> <p>H.3.r.1.b Sender's diagnosis</p> <p>H.1 Narrative case summary and further information</p> <p>H.5 Case narrative in native language</p>
Class of medication error	<p>The appropriate MedDRA LLT (either single term or combination of terms) (see chapter 5.2.2.) should be selected to reflect the class of error (see figure 2).</p> <p>If the class of error cannot be coded with a specific MedDRA LLT, the <i>LLT Medication error</i> should be used and further details on the class of medication</p>	<p>B.2.i.1.b Reaction/ event in MedDRA terminology</p> <p>B.5.3.b Sender's diagnosis</p>	<p>E.i.2.1 Reaction/event</p> <p>H.3.r.1.b Sender's diagnosis</p> <p>H.1 Narrative case</p>

Parameter	Description	ICSR Data element ICH E2B (R2)	ICSR Data element ICH E2B R(3)
	error should be provided in the narrative.	B.5 Narrative	summary and further information H.5 Case narrative in native language
Contributing factor(s)	<p>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:</p> <ul style="list-style-type: none"> • 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, IT software issues etc.; <p>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 4.5.) where appropriate.</p>	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 <i>or</i> H.4 Sender's comments H.5 Case narrative in native language
Medicinal product(s) involved	<p>The medicinal product information should be coded in the ICSR drug section.</p> <p>If the patient did not receive the actual prescribed drug but another one, in ICH E2B (R3) repeatable ICSR sections G should be completed with the information about the prescribed drug and the term '<i>Drug not administered</i>', as well as the information on the dispensed drug as the 'suspect' drug. In ICH E2B (R2) the free text field 'additional information on drug' can also be used. The medication error</p>	B.4.k Drug information B.4.k.1 Characterisation of drug role B.4.k.19 Additional information on	G.k.1 Characterisation of drug role + G.k.2 Drug identification + G.k.10.r Additional

Parameter	Description	ICSR Data element ICH E2B (R2)	ICSR Data element ICH E2B R(3)
	<p>should be captured with the appropriate MedDRA LLT in section E.i Reaction(s)/Event(s).</p> <p>The additional information on drug (coded) data element G.k.10.r should be populated (7=medication error) for ICH E2B (R3).</p>	drug	information on drug
Covariates defining the treated population (CIOMS V)	<ul style="list-style-type: none"> 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 adequate information in the SmPC and package leaflet 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 or package leaflet 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 versus specialist), pregnancy/nursing status, organ impairment 	<p>B.5 Narrative case summary and further information</p> <p>B.5.2 Reporters comments</p> <p>B.5.4 Senders comments</p> <p>B.1.7 Medical history</p> <p>B.3 Tests</p> <p>B.4 Concomitant drugs</p>	<p>H.1 Narrative case summary and further information</p> <p>H.2 Reporter's comments <i>or</i></p> <p>H.4 Sender's comments</p> <p>D.7.1.r.5 Comments +/-</p> <p>D.7.2 Text for relevant medical history and concurrent conditions +/-</p> <p>D.8 Relevant past drug history</p> <p>F.r.2.2.b Test name</p>
Patient outcome	<p>Patient outcome should be recorded for each MedDRA term coded.</p> <p>Patient outcome is not applicable for the medication error itself as the patient cannot recover from the error, only from the clinical consequence(s). There is no ICH E2B data element for 'outcome not applicable', therefore the outcome for the</p>	<p>B.2.i.8 Outcome of reaction/ event at the time of last observation</p>	<p>E.i.7 Outcome of reaction/event at time of last observation</p>

Parameter	Description	ICSR Data element ICH E2B (R2)	ICSR Data element ICH E2B R(3)
	medication error should match the outcome of the associated ADR.		
Seriousness	Coded according to ICSR seriousness criteria (refer to GVP VI.A.2.4): results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is congenital anomaly/birth defect) for serious adverse drug reactions. For non-serious adverse reaction(s) associated with medication errors the patient outcome should be reported accordingly (see patient outcome above).		E.i.3.2 Seriousness criteria at event level
	For medication errors without ADR (i.e. intercepted errors, errors not resulting in harm) and 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 as ICSR in the EU but should be recorded.		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 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 possibility to capture additional information pertinent to the case that is not covered elsewhere in the E2B (R3) data elements under the data element 'Additional Information on Drug (coded) (G.k.10.r)'. This data element provides for coding various scenarios and a drug associated with a medication error may be flagged by populating the data element G.k.10.r with the code number '7' which stands for medication error. The case details still have to be MedDRA coded in the relevant data elements as described in chapter 5.2.2. A business process for using ICH E2B (R3) for recording medication errors in ICSRs is provided in Annex 4.

There may be situations for coding more than one scenario in this data element, for example if a medication error led to unintentional overdose both codes for the medication error (code number '7') and for the overdose (code number '2') should be selected. In addition to the flag a MedDRA LLT should also be provided in data element 'Reaction(s)/Event(s) (E.i.2.1)' selecting the most specific term 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.r.

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 LLT for the associated reaction/event in data element 'Reaction(s)/Event(s) (E.i.2.1)'.

5.6. Rules of anonymisation of personal data

Directive 95/45/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 45/2001¹⁰ regulates the protection of individuals with regard

¹⁰ REGULATION (EC) No 45/2001 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data.

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

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

5.6.1. Healthcare professional reporting

Healthcare professionals are encouraged to report medication errors 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 is not 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.

5.6.2. Potential liability aspects

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

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

There is, therefore, a conflict between this potential liability and the implied pharmacovigilance obligation of the marketing authorisation holder to classify medication errors as such when reporting suspected adverse reactions to national competent authorities or the Agency. This conflict could be potentially addressed by including a 'disclaimer' in the sender's comment data element or the narrative of the ICSR submitted by the marketing authorisation holder to the national competent authority or the Agency:

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

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

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 reaction(s).

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.

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 with medicinal products, including those associated with medication errors, apply.

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 competent authority's attention through exchange agreements with national patient safety organisations as outlined in chapter 6.1.1. 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 apply and promote the classification of medication errors proposed in chapter 4.3.2. to support the performance of pharmacovigilance obligations, i.e. to evaluate medication error reports scientifically, to detect any change to a medicine's benefit-risk balance related to its erroneous use and to implement appropriate risk minimisation measures in a timely and efficient manner.

6.1.1. Collaboration with national patient safety organisations

The EU pharmacovigilance legislation includes legal provisions (chapter 3.) intended to stimulate co-operation between national pharmacovigilance centres and patient safety organisations (PSO) or any other authorities, bodies, organisations and/or institutions responsible for patient safety incident (see definition in chapter 4.4.) reporting and learning systems established in EU Member States. The objective of this collaboration is to minimise preventable harm from medication errors by learning from failures of the healthcare system leading to medication errors.

Many but not all EU Member States have established PSO or national patient safety reporting and learning systems; therefore, the implementation of the legal provisions of Article 107a (5) of Directive 2001/83/EC 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 exists, 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 reporting 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 5. It is acknowledged that individual EU Member States may use different models that best fit their national requirements. In some EU Member States there may be other mechanisms to collect data on medication error outside of hospital settings, for example through poison control centres.

The exchange agreement in figure 5 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 in an appropriate format to allow further processing in national pharmacovigilance databases and subsequent transmission to EudraVigilance by the competent authority.

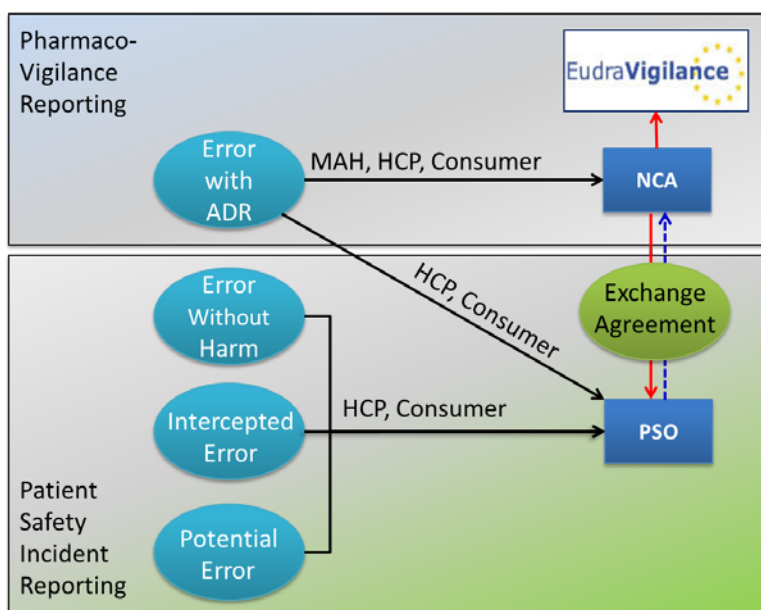


Figure 5: Example of a model for collaboration between National Competent Authorities (NCA) and national patient safety organisations (PSO) for the exchange of medication errors. The red line between NCA and PSO refers to the legal provision to make medication error reports associated with ADR(s) available. The blue dotted line is a good practice recommendation for PSO 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 report¹¹ 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.

¹¹ Reporting and learning systems for medication errors: the role of pharmacovigilance centres. World Health Organisation (2014)

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

In accordance with the EU legislation the Pharmacovigilance and Risk Assessment Committee (PRAC) is responsible for the performance of pharmacovigilance activities, in particular for providing recommendations in relation to the detection, assessment, 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). 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 benefit-risk balance of a medicinal product, based on the evaluation of pharmacovigilance data reported to EudraVigilance and on scientific literature.

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 GVP Module 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.

6.3. The role of healthcare professionals, patients and consumers

Patients, consumers and healthcare professionals are critical stakeholders for successful learning from medication errors acting as primary source and providing first-hand information on the case when reporting medication errors spontaneously to a competent authority, marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre) as unsolicited communication. Healthcare professionals and consumers should be encouraged to provide the most comprehensive case description possible when spontaneously reporting medication errors.

The pharmacovigilance legislation promotes and facilitates adverse reaction reporting by patients, consumers and healthcare professionals through the provision of alternative reporting formats in addition to web-based formats which EU competent authorities provide on their national websites. In this context competent authorities should consider the recommendations¹² for minimum data elements to facilitate the implementation of web-based reporting forms to support consumer reporting of medication errors within their territory.

¹² Reflection Paper on standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients (EMA/137945/2011)

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.

6.4. The role of marketing authorisation holders

GVP VI.C.2.2 describes the responsibilities of marketing authorisation holders in the EU for the collection, recording and reporting of suspected adverse reactions with medicinal products, including those associated with medication errors.

Marketing authorisation holders should also 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.). Such reports should be recorded 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) for summary reports required in PSURs (see chapter 5.4. and Annex 2). This includes reports from literature, solicited reporting and other sources.

Marketing authorisation holders 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 during the development and post-marketing phases, providing information on the circumstances, the potential cause(s) and any mitigating actions 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.

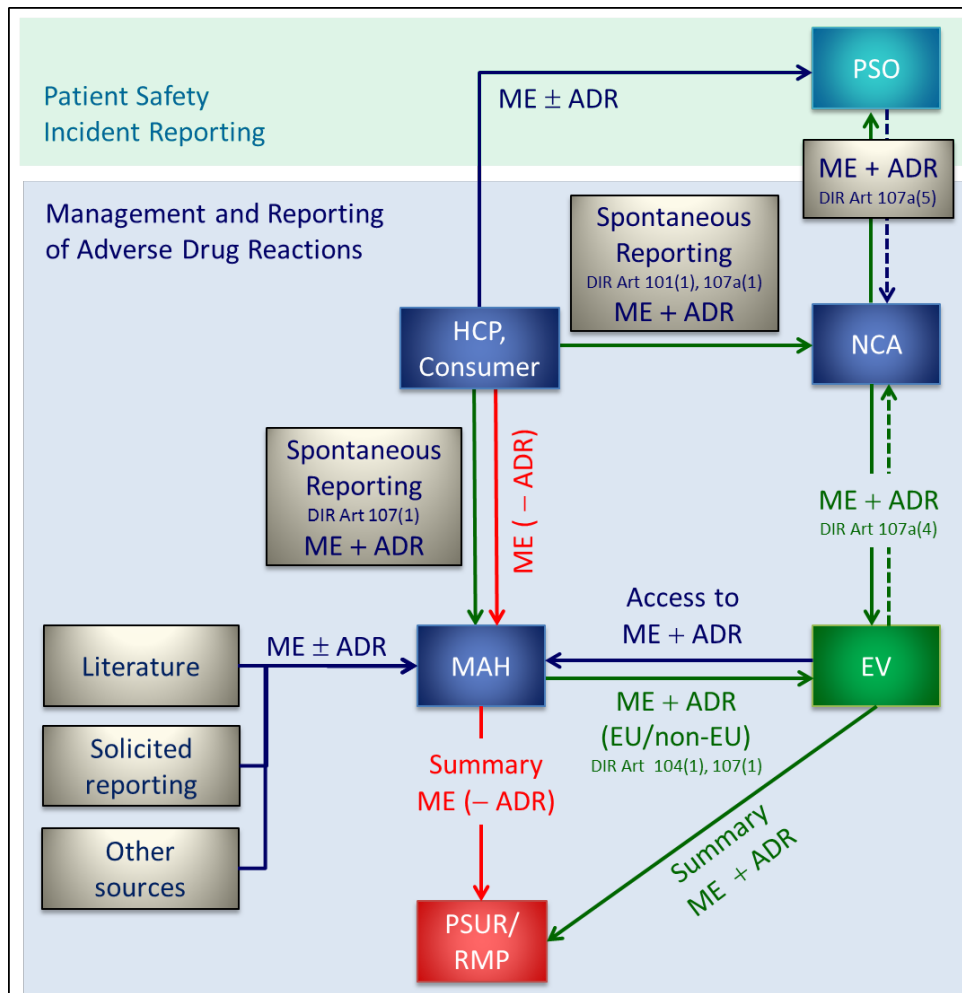
MAH should apply the classification of medication errors referred to in chapter 4.3.2. to facilitate these activities.

List of acronyms

ADR	Adverse reaction
AE	Adverse event
CHMP	Committee for Human Medicinal Products
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
DRP:PTC	MedDRA Data Retrieval and Presentation : Points To Consider
EVDAS	EudraVigilance Data Analysis System
GVP	Good Pharmacovigilance Practice
HCP	Healthcare professional
HLGT	MedDRA High Level Group Term
HLT	MedDRA High Level Term
ICH E2B (R3)	International Conference for Harmonisation E2B (R3) standard
ICSR	Individual case safety report
LLT	MedDRA Lowest Level Term
MAH	Marketing authorisation holder
ME	Medication error
MedDRA	Medical Dictionary for Regulatory Activities
MTS:PTC	MedDRA Term Selection : Points To Consider
NCA	National competent authority
PBRER	Periodic Benefit Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PSO	Patient safety organisation
PSUR	Periodic safety update report
PT	MedDRA Preferred Term
RMP	Risk management plan
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
WHO ICPS	World Health Organisation international classification for patient safety

Annexes

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



The diagram shows the simplified information flow (blue arrows) of medication errors reports and the stakeholders involved: marketing authorisation holders (MAH), national competent authorities (NCA), healthcare professionals and consumers, 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 green arrows represent medication errors reports associated with suspected (serious and non-serious) adverse reactions (+ ADR) in line with EU reporting requirements of Directive 2001/83/EC after a successful EudraVigilance audit. The green dotted arrow represents automatic rerouting of MAH reports from EudraVigilance to NCAs. The red arrows represent medication error reports not associated with suspected adverse reactions (- ADR) brought to the attention of MAHs 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 practice 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 (blue dotted arrow).

Annex 2 - Templates 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 optional templates 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 preferably be created automatically from the pharmacovigilance database and 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 and with oral formulations of the same active substance).

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 allows for aggregation of reported terms in medically meaningful groupings to facilitate analysis of safety data and should be applied for presenting medication errors at MedDRA Preferred Term (PT) and Higher Level Term (HLT) levels based on spontaneous ICSRs as appropriate in line with the provisions in chapter 5.2.

Alternatively, the Standardised MedDRA Query (SMQ) for medication errors referred to in chapter 5.2.10. may be applied once available.

Table A2-1: Template summary tabulation - numbers of Preferred Terms (PT) in the HLT 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 conducted in accordance with Directive 2001/20/EC.

Additional listings of individual cases of medication errors of special interest and medication error not associated with adverse reaction(s) from post-authorisation sources as shown in table A2-2 should only be provided in exceptional circumstances upon request of the competent authority or the Agency

to support the assessment of medication errors in PSURs, particularly medication errors of special interest or if constituting a safety concern in the risk management plan. Listings of individual cases as shown in table A2-2 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: Template listings of individual cases of medication errors of special interest and medication error not associated with adverse reaction(s) from post-authorisation sources*** for <(invented) name>.

Medication error of special interest (MedDRA Preferred Term(s) or class of error)	Reported adverse reaction(s) MedDRA Preferred Term(s) or brief description	Medication stage (prescribing, storing, 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>					
Subtotals					
<PT 2>					
<case 1>					
<case 2>					
Subtotals					
Errors without harm					
<case 1>					
<case 2>					
Subtotals					
Intercepted errors					
<case 1>					
<case 2>					
Subtotals					
Potential errors					
<case 1>					
<case 2>					
Subtotals					

*** 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

This Annex includes specific examples of medication errors with relevance for EU pharmacovigilance reporting requirements which may not reflect current coding practices in all ICH regions. These examples are coded with MedDRA version 18.0 and may not be appropriate for later MedDRA versions.

A) Medication errors reported with clinical consequences

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

Examples

Reported	LLT Term Selected	Comment
Patient was inadvertently administered the higher strength of a calcium channel blocker and experienced hypotension.	<i>Accidental dose increase Hypotension;</i>	
Dose calculation error in an adolescent treated for growth failure results in insulin-like hypoglycaemia.	<i>Dose calculation error; Hypoglycaemia;</i>	
Patient was switched to different insulin product without dose adjustment written on prescription and experienced hypoglycaemia.	<i>Drug prescribing error; Incorrect dose administered Hypoglycaemia;</i>	
Patient was prescribed 10 fold higher strength of an oral opioid and went into respiratory failure at home after having taken 3 doses.	<i>Drug prescribing error; Respiratory failure; Accidental overdose</i>	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.	<i>Drug supply chain interruption; Partial seizures;</i>	
A patient inadvertently used pholcodine for runny nose and complained that their nose was still congested.	<i>Drug ineffective for unapproved indication; Wrong drug administered;</i>	

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

Medication errors without clinical consequences, intercepted errors and potential errors are not reportable as adverse reactions, but as highlighted in chapter 5.4. these cases should also be recorded

by MAHs and NCAs if brought to their attention. Select a term that is closest to the description of medication error reported.

Potential errors may be captured with the LLT *Circumstance or information capable of leading to medication error* and the LLT *Drug not taken in context of intercepted medication error* may apply to situations where an error occurred but it did not actually reach the patient because it was intercepted.

If specifically reported that no adverse effect has occurred, it is possible to select LLT No adverse effect depending on the individual database operation policy.

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.	<i>Product packaging confusion;</i> <i>Wrong drug dispensed;</i>	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.	<i>Inappropriate preparation of medication;</i> <i>Circumstance or information capable of leading to medication error;</i>	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.	<i>Product Label confusion;</i> <i>Circumstance or information capable of leading to medication error;</i>	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.
A three-month-old baby was inadvertently given an ibuprofen syrup quantity measured for a 3-year-old child.	<i>Child product given to infant;</i> <i>Incorrect dosage administered;</i>	Cannot assume an overdose although the inadvertent concept should be represented with an error term.
A father administered one paracetamol suppository to his child without knowing that the child already had received the suppository 10 minutes before.	<i>Extra dose administered;</i>	

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. Some accidental exposures may also be occupational exposures.

Examples

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.	<i>Accidental exposure to product by child;</i>	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.
A dentist accidentally inhaled anaesthetic and passed out.	<i>Accidental exposure to product; Occupational exposure via inhalation of product; Passed out;</i>	Both the accidental and occupational exposure should be captured.

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.

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.	<i>Inappropriate preparation of medication; Accidental overdose;</i>	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'.	<i>Drug administration error; Accidental overdose;</i>	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	<i>Inappropriate dilution of medication; Accidental overdose;</i>	

Reported	LLT Term Selected	Comment
(higher concentrated solution for infusion) with requirements for originator.		

E) Product quality issues

Examples

Reported	LLT Term Selected	Comment
Box contained 2 vials of low strength instead of 1 of high, one of low. Patient used wrong strength and had increased intraocular pressure.	<i>Wrong and correct product strengths in same container; Wrong dose administered; Increased intraocular pressure;</i>	Example of product quality issue (PT product commingling) leading to administration error and adverse effect.
Child swallowed up to 12 tablets due to faulty cap and vomited.	<i>Failure of child resistant mechanism for pharmaceutical product; Accidental exposure to product by child; Vomiting;</i>	Example of product quality issue and medication error with consequence.
Patient noticed tablets didn't look like usual but took anyway and passed out. Later found it was the wrong formulation.	<i>Wrong active ingredient in product; Incorrect product formulation administered Passed out;</i>	The quality issue has resulted in a medication error which reached the patient.

F) Drug delivery device issues

Examples

Reported	LLT Term Selected	Comment
Insulin was given using the wrong syringe resulting in the administration of an overdose. The patient developed hypoglycaemia.	<i>Drug administered in wrong device; Accidental overdose; Hypoglycaemia;</i>	If an overdose is reported in the context of a medication error, the more specific term LLT Accidental overdose can be selected.
Patient experienced paraplegia after an epidural anaesthesia procedure was carried out with a needle contaminated with topical disinfectant.	<i>Device use error Exposure to contaminated device; Paraplegia;</i>	This is a procedural error caused by the wrong use of the epidural needle as device.

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 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. In circumstances where it is clear that it was an unintentional device misuse, LLTs should be selected subordinate to the *PT Device use error*.

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 number '7') if the primary source has clearly stated that a medication error has 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 MTS:PTC).

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	MTS:PTC guidance: do not infer	Disclaimer* may be used as an option	✓

*Disclaimer as referred to in chapter 5.6.2.