



**Federal Agency for Medicines and Health Products
(FAMHP)**

Individual Case Safety Reports (ICSRs) :

new definition of adverse reaction
reporting rules
and others

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Content of the Presentation

1. New ADR definitions

- *Adverse reaction*
- *Overdose - Misuse - abuse - medication error - occupational exposure*

2. Reporting Rules : ‘key changes’

3. Good Vigilance Practice : Module VI : Management and reporting of adverse reactions to medicinal Products (Draft Document)

4. Standard & Format of Pharmacovigilance information : “International Standardisation”

1. *Medicinal Products*
2. *ICSRs*

5. Data Access Policy

6. Data Quality Management

New definitions in pharmacovigilance legislation (I)

New definition of Adverse Reaction (Regulation 1235/2010 Art. 1)

‘a response to a medicinal product which is noxious and unintended’

The directive 2010/84/EU removed the reference to the normal dose since “the term ‘adverse reaction’ should (...) ensure that it 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 the misuse and abuse of a medicinal product” (Recital 5)

This includes also reporting of ADRs not only in normal conditions of use, but also from :

- uses outside terms of Marketing Authorisation : misuse and abuse
- medication error
- overdose
- occupational exposure

No definitions in the legislation but

New definitions in pharmacovigilance legislation (II)

GVP (draft document) defines the following terms :

a. Overdose

This refers to the administration of a **quantity** of a medicinal product given per administration or per day, which is **above the maximal recommended dose** according to the authorised product information. This shall also take into account cumulative effects due to overdose.

b. Misuse

This refers to situations where the medicinal product is **intentionally and inappropriately** used not in accordance with the prescribed or authorised dose, route of administration, and/or the indication(s) or within the legal status of its supply (e.g. without prescription for medicinal products subjects to medical prescription).

c. Abuse

As defined in Article 1 of Directive 2001/83/EC, this relates to the **sporadic or persistent**, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

d. Medication error

This refers to any **unintentional error** in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

e. Occupational exposure

This corresponds to the **exposure** to a medicinal product for human use **as a result of one's occupation**.

Reporting Rules : Key changes (I)

Aim of changing reporting rules :

Better data collection:

- Expedited requirements for non-serious reports
- Patient reporting
- Literature monitoring by EMA
- Medication errors that result in ADRs are collected

Simplified logistics for reporting (after transitional period) :

- All ADRs from MAHs and MSs sent to EV only
- MSs are 'auto-forwarded' their national data
- MAHs access reports in EudraVigilance (EV)

Reporting Rules : Key changes (II)

After transitional period :

Serious/non-serious ADRs should be expeditedly reported :

MAHs shall submit:

- Information on all serious suspected adverse reactions that occur in the EU and in 3rd countries within 15 days
- Non-serious suspected adverse reactions that occur in the EU within 90 days
- ‘Expectedness’ is no longer relevant
- Expedited reporting of non-serious ADRs only for reports originating from EU (3rd countries under discussion)

To Day : as is!

All ICSRs, reportable to FAMHP, should be sent to the EMA's Eudravigilance Database

http://www.fagg-afmps.be/nl/news/news_eudravigilance_avril_2011.jsp

http://www.fagg-afmps.be/fr/news/news_eudravigilance_avril_2011.jsp

http://www.fagg-afmps.be/en/news/news_eudravigilance_avril_2011.jsp

Reporting Rules : Key changes (II)

HCP & patient reports requested :

The MAH shall record all suspected adverse reactions in the EU or in 3rd countries, whether reported spontaneously by patients or HCPs, or occurring in the context of a post-authorisation study

The MAH shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and HCPs

According to current version GVP Module VI:

- **Medical confirmation** should be sought for all patient reports
- MAHs should regularly **screen internet/digital media** (incl. website, blog, chat room, health portal, ...) under their management/responsibility for potential reports of ADRs
- For reports from **Patient Support Programmes** :

_____ Solicited reports : e.g. MAH asks if adverse events were noted with use of product : MAH reports only when there is possible causal relationship as per reporter or MAH

_____ Not-solicited reports : e.g. MAH contacts patient for a refill and is informed of a suspected adverse reaction : MAH should always report the case as this should be considered as a spontaneous report of suspected adverse reaction

Reporting Rules : Key changes (III)

Literature monitoring :

Purpose : avoid duplicate reports in EudraVigilance

The EMA shall:

- Monitor selected medical literature for reports of suspected ADRs to medicinal products containing certain active substances
- Enter identified ICSRs into EudraVigilance
- Publish the list of active substances & medical literature

The MAH shall:

- Not be required to submit the suspected ADRs for medicinal products containing the active substances referred to in the list
- Monitor all other medical literature and report any ADRs

Timeline publication of list selected literature & substances: ??

Reporting Rules : Key changes (III)

Who to who? - rerouting process

To CAs



To MAHs



Rerouting process



Good Vigilance Practice (DRAFT) (I) :

Module VI : Management and reporting of adverse reactions to medicinal Products



EUROPEAN MEDICINES AGENCY

GVP Module VI: Scope

GVP VI addresses the legal requirements detailed in Title IX of Directive 2001/83/EC and Chapter 3 of Regulation (EC) No 726/2004.

GVP VI summarises legal requirements and guidelines applicable to competent authorities in Member States (NCAs), Marketing Authorisation Holders (MAHs) and the Agency as regards the collection, data management and reporting of suspected adverse reactions associated with medicinal products for human use authorised in the European Union (EU) reported by healthcare professionals, patients or consumers.

GVP VI replaces Volume 9A:

- Chapter I.4: Requirements for expedited reporting of ICSRs,
- Chapter I.5: Requirements for reporting in special situations,
- Chapter II.1.3: Management of spontaneous reporting programmes,
- Part III: Electronic exchange of pharmacovigilance information in EU.

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Good Vigilance Practice (DRAFT) (II) :

Module VI : Management and reporting of adverse reactions to medicinal Products



GVP Module VI: Scope

GVP VI provides also recommendations regarding the reporting of suspected adverse reactions occurring in special situations:

- Obligations of the applicant in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation,
- Obligations of MAH following suspension, revocation or withdrawal of a marketing authorisation,
- Reporting in the event of a public health emergency,
- Reporting following the use of a medicinal product during pregnancy or breastfeeding,
- Reporting when a medicinal product is supplied in the context of compassionate use or named patient use,
- Reporting of suspected transmission via a medicinal product of an infectious agent,
- Reporting of lack of efficacy or of suspected adverse reactions related to quality defects or falsified medicinal products,
- Reporting of cases arising from class action law suits.

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Good Vigilance Practice (DRAFT) (III) :

Module VI : Management and reporting of adverse reactions to medicinal Products

GVP Module VI: Structure

Section A: Introduction

- ▶ Definitions relevant for the purpose of GVP VI applicable to Section B and C

Section B: Structures and Processes

- ▶ Agreed principles in relation to the collection, validation, management and reporting of suspected adverse reactions to MPs

Section C: Operation of EU Network

- ▶ EU specific requirements as defined in Reg. and Dir. in relation to suspected adverse reactions to authorized MPs for human use
- ▶ Requirements specific to NCAs in order to encourage reporting from HCPs, patients and consumers
- ▶ Requirements specific to MAHs in relation to MPs for which they hold ownership within or outside EU

Good Vigilance Practice (DRAFT) (IV) :

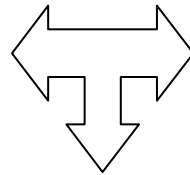
Module VI : Management and reporting of adverse reactions to medicinal Products

Appendixes

- Detailed guidance on the monitoring of scientific and medical literature developed by the Agency
- Detailed guidance on the nullification of cases
- Business process maps and process descriptions in relation to :
 - ▶ Identification of **biological MPs**
 - ▶ Modalities for **expedited reporting** during **interim and final arrangements**,
 - ▶ **Transmission** and **rerouting** to NCAs of ICSRs, transmission to WHO
 - ▶ **Data quality monitoring** of ICSRs transmitted electronically, **duplicate detection** and management of ICSRs.

International Standardisation (I) : general

ICH Steering Committee
decision in 2006
collaborate with
Standard Development
Organisations (SDOs)
for development
of technical standards



At request of the
European
Commission, EMA is
strongly involved in
international
standardisation
activities

Dir 2010/84/EU Article 108:

“...use internationally agreed terminologies,
formats and standards for the conduct of
pharmacovigilance”

Proposed to use ISO formats & standards :

ISO ICSR 27953-2 : Individual Case Safety Report

5 ISO IDMP standards : Identification of Medicinal Products

International Standardisation (II) : art. 57(2) implementation

- The EMA to make public a format for the electronic submission of information on medicinal products for human use by 2 July 2011
- MAHs to electronically submit information to the EMA electronically on all medicinal products for human use authorised or registered in the EU, by 2 July 2012 at the latest, using this format
- MAHs to inform the EMA of any new or varied marketing authorisations granted in the EU using this format

Stepwise 'upgrade' of the EudraVigilance Medicinal Product Dictionary (EVMPD):

- Initial format: EudraVigilance Medicinal Product Report Message
- updated format by end of 2014 to be fully aligned with the 5 ISO Identification of Medicinal Products (IDMP) standards

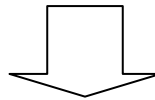
International Standardisation (III) : art. 57(2) implementation

Information to be provided to EudraVigilance Medicinal Product Dictionary initially will include:

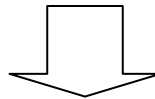
- Description of the (invented) **name**
- Description of the **therapeutic area(s)** e.g. ATC Code
- The designation of **additional monitoring** where applicable
- Description of the **clinical particulars** i.e. therapeutic indication(s)
- Details of the **MAH**
- Details of the **marketing authorisation**, including authorisation date, marketing status, Marketing authorisation procedure
- Country of marketing authorisation + MAH number
- Mutual-recognition **procedure** number / decentralised-procedure number
- Orphan drug designation
- Detailed description of the **active substance(s)**, **excipient(s)**, **adjuvant(s)** and their specific characteristics
- Description of the packaging information
- Electronic copy of the **SPC, Package Leaflet** and annexes for CAPs)

International Standardisation (I) : art. 57(2) implementation.... BUT....

Concerns raised by MAHs : short timeline, high workload,
availability of IT-tools, content (Structured
Substance Information),



EMA workshop with European pharmaceutical
industry associations (Jan 2012)



- Reduction of mandatory data compared to July 2011
description of packaging information
location of PhVSMF
regulated documents (condition of MA, PL)
- Structured Substance Information: not to be submitted until
agreement is reached
- SPC to be submitted for validation purposes

**Stepwise approach to move forwards ISO IDMP
implementation as ultimate and longer term objective**

International Standardisation (I) : art. 57(2) implementation.... BUT....

- Revised format published on 5 March 2012
- Significantly reduces the administrative burden and helps MAHs to meet their legal deadline of 2 July 2012



The screenshot shows the EMA website interface. At the top, it says 'An Agency of the European Union' with the EU flag. The main header includes the EMA logo and the text 'EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH'. There is a search bar and text size options. The navigation menu includes 'Home', 'Find medicine', 'Regulatory' (highlighted), 'Special topics', 'Document search', 'News & events', 'Partners & networks', 'About us', and 'Quick links'. The left sidebar lists 'Human medicines' with sub-items: Pre-authorisation, Post-opinion, Post-authorisation, Product information, Scientific advice and protocol assistance, Scientific guidelines, Innovation Task Force, and Regulatory and... The main content area shows a breadcrumb trail: 'Home > Regulatory > Human medicines > Pharmacovigilance > 2010 pharmacovigilance legislation > Electronic submission of information on medicines > Electronic submission documents'. The title is 'Documents for electronic submission of information on medicines'. Below the title, it says 'This page lists the documents related to the electronic submission of information on medicines by marketing-authorisation holders'. A 'Table of contents' is provided with links to 'Legal notice', 'Article 57(2) requirements: Frequently asked questions', 'Detailed guidance on electronic submission of information on medicinal products', and 'Controlled vocabularies'.

Link: www.ema.europa.eu : [Home](#) ► [News and Events](#) ► [News and press release archive](#)
or <http://eudravigilance.ema.europa.eu/human/index.asp>

Eudravigilance Data Access Policy (I)

Full access to EEA Competent Authorities of the Member States, to the Agency and the Commission

Partial Access to be implemented for HCPs, patients and consumers

- Data set for spontaneous reports
- Compliance with EU personal data protection legislation

Access for marketing authorisation holders planned as follows:

- Data set for spontaneous reports
- Compliance with EU personal data protection legislation
- Access to EudraVigilance Data Warehouse and Analysis
- System (EVDAS) and data analysis and signal detection tools
- Results of EVDAS queries to be downloadable and printable either in aggregated format (e.g. as tabular or graphic presentations, line listings) or as individual report forms
- Downloads in ICH E2B format and in accordance with the ICH M2 message specifications

Access to research organisations planned

Eudravigilance Data Access Policy (II)



EudraVigilance Access Policy Overview (4)

	ACCESS TO	ACCESS VIA
NCA's, EC, EMA	all data fields	Data warehouse (EVDAS) → signal detection and data analysis functionalities
MAHs & Sponsors	- all data fields if sender - defined data fields* if not sender	
Research Organisations	defined data fields*	
HCPs & general public	defined data fields*	Dashboards (website) → aggregated reports

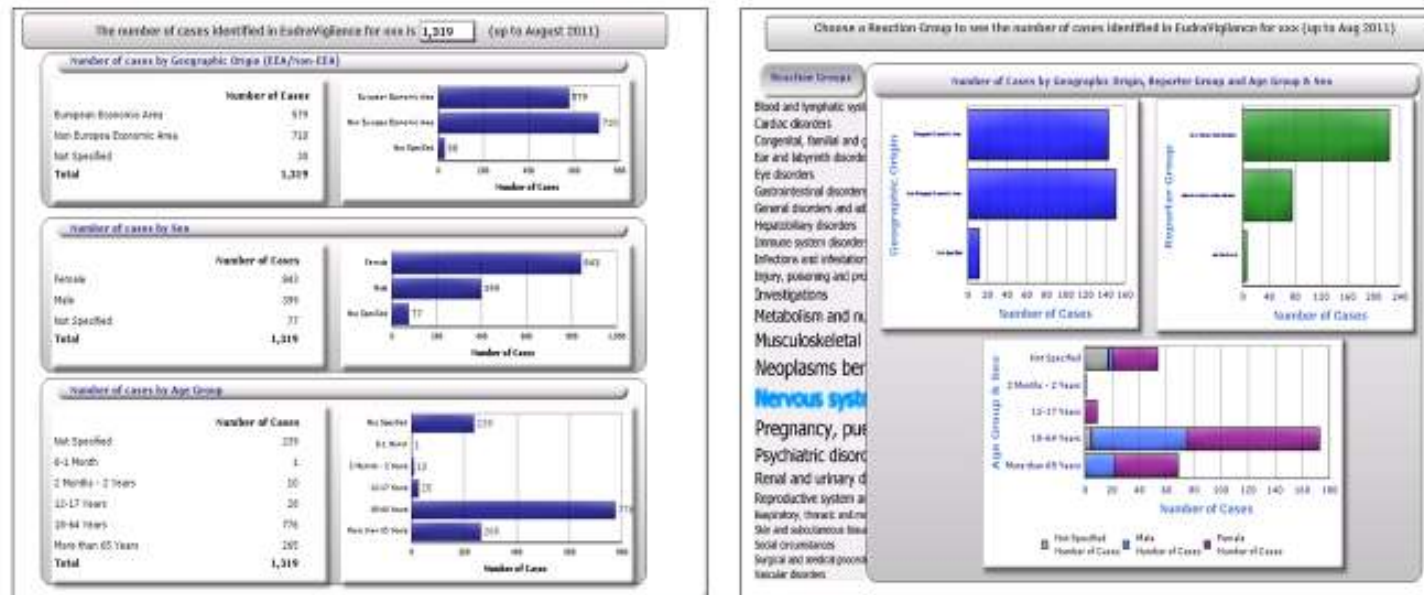
* Set of defined data fields available in the EV Access Policy document

Eudravigilance Data Access Policy (III)



EudraVigilance Access Policy Implementation (5)

The dashboard provide functionalities for the user to navigate within multiple panels, refining at the same time the level of information provided



EudraVigilance Data Quality Management (I)

Functionalities to support the operation of procedures that ensure quality and integrity of the information collected in EudraVigilance :

- Validation of ICSRs against defined business rules
 - Duplicate detection and management
 - Coding of product information
 - ICSR data quality review
-
- Important for conduct of signal detection and benefit risk assessment
 - Ensure that accurate and reliable data held in EudraVigilance are made available (EudraVigilance Access Policy)

Eudravigilance Data Quality Management (I)



EudraVigilance Access Policy Data Quality (1)

In accordance with decisions taken by the Heads of Medicines Agencies in April 2008, the EMA has been undertaking work to clean and code the data in EudraVigilance prior to implementation of the EV Data Access Policy and pre-emptive release of data to the public

Work Package	Objective
WP1 - Detection and management of duplicate ICSRs	'merge' all confirmed duplicated reports
WP2 - Manual recoding of medicinal products reported in ICSRs	'code' all medicinal products to assist signal detection activities
WP3 - Validate and update the medicinal products in the EudraVigilance Medicinal Product Dictionary (EVMPD)	have a reliable coding thesaurus
WP4 - Review the quality of ICSRs reported to EudraVigilance	improve overall quality of the data submitted by providing feedback to the reporting organisations
WP5 - The provision of translation of case narratives and medicinal product information	assist the review of case narratives where an English summary is not provided as defined in Volume 9A, part III

Timelines
✓ Started in Dec 2010 > All duplicates should be screened and cleaned by July 2012
✓ Started in Dec 2010 > All medicinal product information reported in ICSRs should be recoded by end Q1 2012
✦ To start Q1 2012 according to current forecasts
✓ Started in Jun 2011 > Approx. 100 sender organisations will have been reviewed and contacted by end-2011



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Information related to ICSRs

Legislation :

- [Directive 2010/84/EU](#) : nationally authorised products
- [Regulation \(EU\) No 1235/2010](#) : centrally authorised products & EMA tasks

Link : www.ema.europa.eu : [Home](#) ► [Special Topics](#) ► 2010 pharmacovigilance legislation (Upper part)

Guidance :

Good pharmacovigilance practices (GVP) (DRAFT)

Link : www.ema.europa.eu : [Home](#) ► [Regulatory](#) ► [Human medicines](#) ► [Pharmacovigilance](#) ► [2010 pharmacovigilance legislation](#) ► Good pharmacovigilance practices

EMA's Stakeholder events :

The EMA is hosting a series of **stakeholder meetings** during 2011 and 2012, aiming to raise awareness of the requirements of the new legislation and promote the exchange of ideas, concerns and opinions.

Link : www.ema.europa.eu : [Home](#) ► [Special Topics](#) ► 2010 pharmacovigilance legislation (lower part)

Information related to international standardisation

Set of 5 ISO IDMP standards : final documents expected end 2012 :

- **ISO prEN 11615**, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of regulated medicinal product information'
- **ISO prEN 11616**, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of regulated pharmaceutical product information'
- ISO prEN 11238**, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of regulated information on substances'
- **ISO prEN 11239**, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging'
- **ISO prEN 11240**, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of units of measurement'

ISO ICSR standard : final document : end 2011 :

- **ISO prEN 27953-2**, Health Informatics 'Individual Case Safety Reports' for the electronic transmission of suspected adverse reactions

<http://www.hl7.org/> ► Home ► Project Summary for IDMP Terminologies Project (JIC Project)