Novità europee e italiane in tema di farmacovigilanza: Il New Eudravigilance System e il conseguente impatto a livello nazionale

Roma 18 Ottobre 2017
Having considered the independent audit report and the PRAC recommendation, the EMA Management Board confirms that the EudraVigilance database has achieved full functionality and that the system meets the functional specifications drawn up pursuant to Article 24(2) first subparagraph of Regulation (EC) No 726/2004.
In summary, the simplified electronic reporting of suspected adverse reactions related to medicines by National Competent Authorities and marketing authorisation holders to EudraVigilance becomes mandatory six months after the functionalities of the EudraVigilance database have been established and have been announced by the Agency i.e.
### Benefits of the new EudraVigilance system

<table>
<thead>
<tr>
<th>New features</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced <strong>signal-detection</strong> and data-analysis tools to support safety</td>
<td>Better detection of new or changing safety issues, enabling rapid action to protect public health</td>
</tr>
<tr>
<td>monitoring directly by Member States and marketing authorisation holders</td>
<td></td>
</tr>
<tr>
<td>Improved <strong>quality and completeness of ICSR data</strong></td>
<td>Better searchability and more efficient data analysis</td>
</tr>
<tr>
<td>Enhanced <strong>scalability</strong> of the EudraVigilance system</td>
<td>Able to support an increased number of ICSRs due to the new requirement to report non-serious cases to EudraVigilance</td>
</tr>
</tbody>
</table>
## Benefits of the new EudraVigilance system

<table>
<thead>
<tr>
<th>New features</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplified reporting of ICSRs to EudraVigilance and the rerouting of ICSRs to Member States</td>
<td>Reduced duplication of efforts</td>
</tr>
<tr>
<td></td>
<td>Marketing authorisation holders no longer have to provide ICSRs to national competent authorities, they have to submit these to EudraVigilance only</td>
</tr>
<tr>
<td>EMA will provide data to the World Health Organization (WHO) Uppsala Monitoring Centre directly from EudraVigilance</td>
<td>Enhanced collaboration between EMA and WHO</td>
</tr>
<tr>
<td></td>
<td>Member States will no longer need to carry out this task</td>
</tr>
</tbody>
</table>
Perché il potenziamento di Eudravigilance?

Il potenziamento di EudraVigilance si è reso necessario per supportare i significativi cambiamenti introdotti dalla nuova normativa europea di farmacovigilanza in termini di requisiti per la segnalazione delle sospette reazioni avverse (ADRs).

La nuova versione di Eudravigilance diventerà operativa il 22 novembre 2017 ed entro questo termine le autorità competenti nazionali e i titolari di autorizzazione all’immissione in commercio, devono organizzarsi per garantire che i loro processi e le infrastrutture IT locali siano compatibili con il nuovo sistema e con il nuovo formato concordato a livello internazionale.
Technical changes to the EV system

- Implementation of the new ISO ICSR format (R3) for the submission and exchange of ICSRs

- Migrating all existing ICH E2B(R2) ICSR data to the new ICH ICSR format (R3)

- Redesign of EVWEB, the web application for the electronic reporting and management of ICSRs

- Introducing new functionalities in the EudraVigilance data analysis system (EVDAS)
Technical changes to the EV system

Two new functionalities to the system

• EudraVigilance rerouting functionality, which defines the rules for the forwarding of ICSRs to the national competent authority (NCA) where the adverse reaction occurred (rules can be set by NCAs according to their needs and preferences);

• ICSR download functionality to enable marketing authorisation holders to download ICSRs concerning their products or ICSRs reported with a substance for which they hold a marketing authorisation in the EEA.
From 22 Nov 2017 the centralised reporting to EV will be implemented and therefore MAHs will not receive the ICSRs from the NCAs.

MAHs will have access to EudraVigilance to retrieve those cases.

Those cases will be accessible via EVWEB:

- Access is per substance
- Prospective cases only (from 22 Nov 2017)
- EEA cases only
Eudravigilance

EudraVigilance WEB reporting application
EVWEB
- ICSR creation
- ICSR submission
- ICSR query
- MAH ICSR download (*EVPM)
- NCA ICSR rerouting

EudraVigilance database management system
EVDBMS
- EudraVigilance post-authorisation module (EVPM)
- EudraVigilance clinical trials module (EVCTM)

Extraction, transformation and loading process ETL
Re-coding
Duplicate detection

EudraVigilance data warehouse and analysis system
EVDAS
- Signal detection
- Data analysis

European database of suspected adverse drug reaction reports
Adrreports.eu

MedDRA and standard terminology
Medicinal products (Art 57 database/XEVMPD)
EV organisation and user management

Key
- Data collection
- Data management
- Data analysis
- Standard terminology
- Security management
A transition period is foreseen in which both E2B(R2) and E2B(R3) files can be exchanged. However, several rules are applied during this period:

- for E2B(R2) ICSRs, E2B(R2) acks will be returned by EV
- for E2B(R3) ICSRs, E2B(R3) acks will be returned by EV
- EVWEB 8 generates E2B(R3) only
- Web Trader Post-function Traders and Gateway Traders can submit both E2B(R2) or E2B(R3) files
- Once an organisation switches from E2B(R2) to E2B(R3), no switching back to E2B(R2) is allowed.
Eudravigilance High Level Plan

High level plan of changes

<table>
<thead>
<tr>
<th>Key milestones</th>
<th>2016</th>
<th>2017</th>
<th>Post ISO IDMP Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Revised EV Access Policy published</td>
<td>EudraVigilance Audit</td>
<td>EV stop accepting R2 format messages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Announcement of successful EudraVigilance Audit</td>
<td>6 months post announcement of successful audit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 2017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EV start accepting R3 format messages</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implement ICSR routing changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implement EV Access Policy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implement new EVDAS/eMR functionalities</td>
<td></td>
</tr>
</tbody>
</table>
Business processes changes

- Marketing authorisation holders will no longer provide ICSRs to national competent authorities and must submit these to EudraVigilance only.

- Marketing authorisation holders will have a legal obligation to monitor the data available in EudraVigilance and inform EMA or national competent authorities of any safety signals identified. EMA will grant marketing authorisation holders access to EVDAS to use signal detection, analytical and reporting functions to the extent necessary to fulfil their obligation.

- Following the switch to simplified reporting, EMA will submit ICSRs through EudraVigilance to the WHO Uppsala Monitoring Centre, rather than national competent authorities doing this;
Guideline on good pharmacovigilance practices (GVP) Module VI – Rev 2

<table>
<thead>
<tr>
<th>Document(s)</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
<th>Effective Date</th>
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</thead>
<tbody>
<tr>
<td>Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)</td>
<td>(English only)</td>
<td>adopted</td>
<td>25/06/2012</td>
<td>02/08/2017</td>
<td>22/11/2017</td>
</tr>
</tbody>
</table>

22 November 2017
Guideline on good pharmacovigilance practices (GVP) Module VI – Rev 2

The guidance applies to

- Medicinal products for human use authorised in the EU
- Homeopathic and herbal medicinal products with the exception of homeopathic medicinal products authorised under the special simplified registration procedure detailed in Article 14 (1) of Directive 2001/83/EC [DIR Art 16 (3) and Art 16g], and to
- Medicinal products supplied in the context of compassionate use as defined in Article 83(2) of Regulation (EC) No 726/2004, subject to and without prejudice to the applicable national laws of EU Member States. As the case may be, this guidance may also apply to named patient use as defined under Article 5(1) of Directive 2001/83/EC
Downtime di Eudravigilance

• Certain key EudraVigilance functionalities will be entirely or partially unavailable for ten working days from 8 to 21 November 2017, to enable EMA to release an enhanced Eudravigilance system on 22 November 2017.

• The EudraVigilance web application (EVWEB) for electronic reporting of ICSRs and suspected unexpected serious adverse reactions (SUSARs) will be unavailable.

• The extended EudraVigilance medicinal product dictionary (XEVMPD, also known as the Article 57 database) for the electronic submission of data on medicines will be unavailable.
Downtime di Eudravigilance

EudraVigilance Go-Live Plan
Steps to be followed by national competent authorities, marketing authorisation holders and sponsors of clinical trials in the EEA

EudraVigilance Access Policy

• Compliance with personal data protection requirements as set out in Regulation (EC) No 45/2001 and Directive 95/46/EC.

Entry into force

• This Access Policy will enter into force six months following the announcement by the Management Board of the Agency that based on an independent audit report the EudraVigilance database has achieved full functionality.

22 November 2017
Access Group

Stakeholder Groups

1. Medicines regulatory authorities in EEA Member States, the European Commission and the Agency (Group I)
2. Healthcare Professionals and the Public (Group II)
3. Marketing Authorisation Holders (Group III)
4. Academia (Group IV)
5. WHO – Uppsala Monitoring Centre (Group V)
6. Medicines regulatory authorities in third countries (Group VI)
## Access level

<table>
<thead>
<tr>
<th>Access Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>- Public subset of ICSR data elements with main focus on&lt;br&gt;- Stakeholder groups II, III, IV, V and VI.</td>
</tr>
<tr>
<td></td>
<td>- Extended subset of ICSR data elements with main focus on&lt;br&gt;- Stakeholder group III to fulfil their pharmacovigilance obligations.&lt;br&gt;- Stakeholder group IV to directly advance public health and work, which is intended to improve procedures for protecting public health.</td>
</tr>
<tr>
<td>Level 2A</td>
<td>- Extended subset of ICSR data elements including case narratives with main focus on&lt;br&gt;- Stakeholder group III to validate signals.</td>
</tr>
<tr>
<td>Level 2B</td>
<td>- Extended subset of ICSR data elements with main focus on&lt;br&gt;- Stakeholder group V and VI thus fostering protection of public health outside the EEA.</td>
</tr>
<tr>
<td>Level 3</td>
<td>- All ICSR data elements without restrictions with main focus on&lt;br&gt;- Stakeholder group I taking into account their roles and responsibilities to protect public health.&lt;br&gt;- Stakeholder group III to fulfil their pharmacovigilance obligations based on the ICSRs that a MAH has sent to EudraVigilance or on ICSRs resulting from the medical literature monitoring activities performed by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004.</td>
</tr>
<tr>
<td>ICH E2B(R3) ICSR Implementation Guide ICSR sections</td>
<td>Total</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>C.1 Identification of the case safety report</td>
<td>20</td>
</tr>
<tr>
<td>C.2.r Primary source(s) of information</td>
<td>15</td>
</tr>
<tr>
<td>C.3 Information on sender of case safety information</td>
<td>16</td>
</tr>
<tr>
<td>C.4.r Literature reference(s)</td>
<td>2</td>
</tr>
<tr>
<td>C.5 Study identification</td>
<td>6</td>
</tr>
<tr>
<td>D. Patient characteristics</td>
<td>96</td>
</tr>
<tr>
<td>E.1 Reaction(s)/event(s)</td>
<td>21</td>
</tr>
<tr>
<td>F.1 Results of tests and procedures relevant to the investigation of the Patient</td>
<td>13</td>
</tr>
<tr>
<td>G.1 Drug(s) information</td>
<td>76</td>
</tr>
<tr>
<td>H. Narrative case summary and further information</td>
<td>7</td>
</tr>
<tr>
<td>Grand Total</td>
<td>272</td>
</tr>
</tbody>
</table>
Since May 2012, healthcare professionals, the public, MAHs and academia have certain levels of access to spontaneous reports focusing on centrally authorised medicinal products.

This access is provided through the adrreports.eu portal of the Agency and was extended in September 2014 to all active substances contained in medicinal products authorised in the EEA.
The number of individual cases identified in EudraVigilance for ACLAsta is 10,885 (up to May 2017).

### Number of Individual Cases by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Specified</td>
<td>1,249</td>
<td>11.5%</td>
</tr>
<tr>
<td>0-1 Month</td>
<td>1</td>
<td>0.0%</td>
</tr>
<tr>
<td>2 Months - 2 Years</td>
<td>1</td>
<td>0.0%</td>
</tr>
<tr>
<td>3-11 Years</td>
<td>3</td>
<td>0.0%</td>
</tr>
<tr>
<td>12-17 Years</td>
<td>3</td>
<td>0.0%</td>
</tr>
<tr>
<td>18-64 Years</td>
<td>2,568</td>
<td>23.6%</td>
</tr>
<tr>
<td>65-85 Years</td>
<td>5,690</td>
<td>52.3%</td>
</tr>
<tr>
<td>More than 85 Years</td>
<td>1,270</td>
<td>12.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10,885</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

### Number of Individual Cases by Sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>9,195</td>
<td>84.5%</td>
</tr>
<tr>
<td>Male</td>
<td>1,476</td>
<td>13.6%</td>
</tr>
<tr>
<td>Not Specified</td>
<td>214</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10,885</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

### Number of Individual Cases by Geographic Origin (EEA/Non-EEA)

<table>
<thead>
<tr>
<th>Occurrence Country EEA/Non EEA</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Economic Area</td>
<td>2,120</td>
<td>19.8%</td>
</tr>
<tr>
<td>Non European Economic Area</td>
<td>8,765</td>
<td>80.5%</td>
</tr>
<tr>
<td>Not Specified</td>
<td>91</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10,885</td>
<td>100.0%</td>
</tr>
<tr>
<td>Document(s)</td>
<td>Language</td>
<td>Status</td>
</tr>
<tr>
<td>-------------</td>
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<td>---------</td>
</tr>
<tr>
<td>Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management (Rev. 1)</td>
<td>(English only)</td>
<td>adopted</td>
</tr>
</tbody>
</table>

22 November 2017
Signal Management
Transitional arrangements for MAHs

During a pilot period of one year, only MAHs whose active substances are included in the list of medicines under additional monitoring on 22 November 2017 will be asked to monitor EudraVigilance and inform EMA and national competent authorities of validated signals with their medicines.

This requirement will only start on 22 February 2018, effectively granting those MAHs a three-month 'grace period' to familiarise themselves with the new EudraVigilance system, the new tools to support EudraVigilance monitoring and to finalise their own processes.
Signal Management
Transitional arrangements for MAHs

EMA will publish further information on the practical aspects of the pilot period before it begins.

All other MAHs will also have access to EudraVigilance data and will be able to integrate the data into their own signal management processes. However, during the pilot period they will have no obligation to continuously monitor EudraVigilance and inform the regulatory authorities of validated signals.

After one year, EMA will base the next phase of implementation on experience gained through the pilot.
Principali cambiamenti sul sistema nazionale di FV

1. Business Process -> Gestione segnalazioni e segnali

2. Infrastruttura IT -> Rete Nazionale di Farmacovigilanza
Modifiche di business process a livello nazionale

1. Misure di transizione e quando esse terminano
2. Gestione del periodo di downtime di Eudravigilance
3. Nuove disposizioni in tema di gestione delle segnalazioni
4. Controllo dei duplicati in RNF
5. Gestione dei follow-up
6. Type of reports / Segnalazioni da studi osservazionali
7. Emerging Safety Issues
8. Standalone signal notification
Il sistema di segnalazione italiano
Disposizioni transitorie valide fino al 21/11/2017

Option C → MAH

Option A → Person Responsible for PhV → 7 days → MAH

Option B → www.vigifarmaco.it → National PhV Network

Reporter: Within 36h or 2 days

7 days → Option C
15/90 days Monthly

www.vigifarmaco.it
Downtime di Eudravigilance

3 October 2017
EMA/399493/2017
Inspections, Human Medicines Pharmacovigilance & Committees

EudraVigilance Go-Live Plan
Steps to be followed by national competent authorities, marketing authorisation holders and sponsors of clinical trials in the EEA

Downtime di EudraVigilance (EVPM) - Italy

- Until 21 (24:00) November 2017, AIFA will continue to receive the cases directly in its national pharmacovigilance database (NPhVD) as foreseen by the transitional (interim) reporting measures set out in GVP Module VI revision 1.

- After the cutover period, AIFA will send all cases registered in the NPhVD from 8-21 November directly to EudraVigilance within the 2 business days.

- For AIFA the new simplified reporting rules will be applied from 22/11/2017.

- The Italian Agency will stop sending ICSRs to WHO UMC as of 8 (00:00) November 2017.
Gestione del downtime period di Eudravigilance

- Prima del downtime di EV, l’ultimo invio di segnalazioni dalla RNF a EV avverrà il 07/11/2017 e riguarderà le segnalazioni (gravi e non gravi) inserite nella RNF al 06/11/2017 ore 23:59

- Il 22/11/2017 alle 10:00 ora italiana riprenderà la trasmissione dalla RNF a EV per le segnalazioni inserite nella RNF dalle 00:01 del 07/11/2017 alle 23:59 del 21/11/2017
The Italian Agency AIFA (HQ ORG-ID MINISAL02, affiliate AI FACT) will stop receiving ICSRs from sponsors from 8 (00:00) to 21 (24:00) November 2017.

SUSAR reports in CIOMS I format and line listings should be transmitted by email: SUSAR_ITA@aifa.mailcert.it

From 22/11/2017, the SUSAR sent to SUSAR_ITA@aifa.mailcert.it during the cutover period, shall be submitted to EVCTM from the sponsors.
4. Fino a quando l’EMA non potrà assicurare le funzionalità della banca dati Eudravigilance di cui all’art. 24 del regolamento (CE) n. 726/2004......

5. Fino a quando l’EMA non potrà assicurare le funzionalità della banca dati Eudravigilance di cui all’art. 24 del regolamento (CE) n. 726/2004......

22 Novembre 2017: Terminano le disposizioni transitorie previste dall’art 45 del DM 30/04/2017 commi 4 e 5
22 Novembre 2017
entrano in vigore le nuove disposizioni italiane di *Simplified Electronic Reporting*
Art. 24 comma 9 del DM 30 aprile 2015:
L’AIFA non impone ai titolari delle autorizzazioni all’immissione in commercio alcun obbligo supplementare per la segnalazione di sospette reazioni avverse, a meno che non vi siano motivi giustificabili connessi alle attività di farmacovigilanza.

Art. 107 bis comma 6 della Direttiva 2010/84/EU:
A meno che vi siano motivi giustificabili connessi alle attività di farmacovigilanza, i singoli Stati membri non impongono ai titolari delle autorizzazioni all’immissione in commercio alcuna obbligazione supplementare per la segnalazione di sospetti effetti collaterali negativi.
D.M. 30.04.2015 – Art. 23 commi 4 e 5

4. …… i titolari dell'AIC trasmettono per via elettronica alla banca dati Eudravigilance informazioni su tutte le sospette reazioni avverse gravi che si verificano nell'Unione e nei Paesi terzi entro i 15 giorni solari successivi al giorno in cui il titolare dell'AIC interessato viene a conoscenza dell'evento.

5. …… i titolari dell'AIC trasmettono per via elettronica alla banca dati Eudravigilance informazioni sulle sospette reazioni avverse non gravi che si verificano nell'Unione entro i 90 giorni solari successivi al giorno in cui il titolare dell'AIC interessato viene a conoscenza dell'evento.

<table>
<thead>
<tr>
<th></th>
<th>UE</th>
<th>Extra UE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravi – 15 gg</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Non Gravi – 90 gg</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>
I titolari di AIC non saranno più tenuti a inviare le segnalazioni di sospette ADRs alle autorità nazionali competenti (nel caso specifico all’AIFA/Responsabili di FV locali), ma dovranno trasmetterle direttamente ad EudraVigilance che, attraverso la funzione di “re-routing” le inoltrerà alle autorità nazionali competenti.

Questo comporterà che per ogni autorità nazionale ci sarà un flusso di dati da e verso Eudravigilance, in modo da assicurare la completezza sia dei database nazionali che di quello europeo che diventerà il central repository per le segnalazioni di sospette reazioni avverse a medicinali autorizzati o in fase di studio nell'EEA.
Aumento della capacità di Eudravigilance di gestire grandi quantità di documenti e utenti

- Gli obblighi di inviare a Eudravigilance le segnalazioni di sospette reazioni avverse non riguarderanno più solo i casi gravi ma anche quelli non gravi verificatisi nella EEA.

- In previsione pertanto di un considerevole aumento dei dati da gestire, la capacità di Eudravigilance di supportare grandi quantità di dati è stata potenziata. Il sistema aggiornato inoltre offrirà strumenti di ricerca migliori e una più efficiente capacità di analisi dei dati.
Italian Simplified Electronic Reporting

Operatori sanitari e cittadini

Rimane invariata la segnalazione delle sospette reazioni avverse da parte dei pazienti e degli operatori sanitari alle autorità nazionali competenti secondo le consuete modalità:

- o Responsabili di FV della struttura sanitaria di appartenenza
- o Vigifarmaco (sistema segnalazione on-line)
- o Titolare AIC
Le autorità nazionali dei singoli Stati membri non dovranno più inviare le proprie segnalazioni di sospette reazioni all'Uppsala Monitoring Centre (UMC) dell'OMS, perché sarà l'EMA ad occuparsi di questo inviando direttamente i dati da EudraVigilance.
When one party (competent authority or a marketing authorisation holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the valid report should still be submitted as ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR.

Questo significa che i titolari AIC sono tenuti a inserire in Eudravigilance qualsiasi segnalazione in loro possesso ad eccezione di quelle di cui vengono a conoscenza per il tramite della RNF.
Il nuovo sistema di segnalazione italiano

Reporter:
Within 36h or 2 days

Option C MAH

Person Responsible for PhV

Option A

Option B www.vigifarmaco.it

Online!

7 days

15/90 days Monthly

National PhV Network

MAH Region

Monthly

EudraVigilance
Il nuovo sistema di segnalazione italiano

Option A → Resp PhV → 7 days → CRFV Region

Option B → www.vigifarmaco.it → National PhV Network

Option C → MAH → 15/90 days → EudraVigilance → Uppsala Monitoring Centre

Reporter: Within 36h or 2 days

Every night

RE-ROUTING

DOWNLOAD
Controllo dei duplicati in RNF da parte dei Responsabili di FV locali e CRFV

In considerazione del re-routing, ovvero delle segnalazioni che perverranno nella RNF direttamente da Eudravigilance, ai Responsabili di FV locali (ASL, Aziende Ospedaliere, I RCSS e Centri Regionali di FV), prima di un qualsiasi inserimento di segnalazione nella RNF, è richiesto di verificare che essa non sia già presente in RNF.
Responsabili di FV locali e CRFV

!! E' fondamentale il rispetto delle tempistiche previste a livello normativo per l'inserimento/validazione delle schede di segnalazione in RNF

Resp PhV

7 days

Rete Nazionale di Farmacovigilanza
Validation of reports

Minimum Criteria:
1. One or more identifiable reporter (Qualification – Country)
2. One single identifiable patient
3. One or more suspected substance/ medicinal product
4. One or more suspected adverse reaction*

*If the primary source has made an explicit statement that a causal relationship between the medicinal product and the reported adverse event has been excluded and the notified competent authority or marketing authorisation holder agrees with this assessment, the report does not qualify as a valid ICSR since the minimum information for validation is incomplete (there is no suspected adverse reaction).

!! Only valid ICSRs should be submitted
Follow-up of reports – GVP VI

When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for

- monitored events of special interest,
- prospective reports of pregnancy (see VI.B.6.1. for guidance on the management of pregnancy reports),
- cases notifying the death of a patient,
- or cases reporting new risks or changes in the known risks.

This is in addition to any effort to collect missing minimum criteria for reports validation (see VI.B.2. for ICSRs validation). Any attempt to obtain follow-up information should be documented.
Follow-up of reports – GVP VI

Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern.

The use of targeted specific forms in the local language should avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting.

Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source easy.
Follow-up of reports – GVP VI

When information is received directly from a consumer suggesting that an adverse reaction may have occurred, and if the information is incomplete, attempts should be made to follow-up with the consumer to obtain consent to contact a nominated healthcare professional to obtain further information.

When the case is subsequently confirmed totally or partially by a healthcare professional, the medical confirmation should be captured in the ICSR in line with ICH-E2B (see VI.A.1.4. for healthcare professionals’ definition, and VI.A.1.5. for ICSRs medical confirmation).
A valid case of suspected adverse reaction initially notified by a consumer cannot be downgraded to a report of non-related adverse event if a contacted healthcare professional (nominated by the consumer for follow-up information) subsequently disagrees with the consumer’s suspicion (see VI.A.1.1. for causality definition). In this situation, the opinions of both the consumer and the healthcare professional should be detailed in the narrative section of the ICSR.

The same principle applies to the ICSR seriousness criterion, which should not be downgraded from serious to non-serious if the notified recipient disagrees with the seriousness reported by the primary source.
Follow-up - GVP VI

For the ICSRs made accessible to a MAH from the EudraVigilance database the routine request for follow-up by the marketing authorisation holder is not foreseen. If the follow-up of an ICSR is necessary for a specific situation, a justification should be provided with the request, which should be addressed directly to the sender organisation of the ICSR.

Per i casi italiani, la sender organisation è rappresentata dall’AIFA ovvero dalla RNF, e le eventuali richieste di follow-up, con la relativa giustificazione, devono essere inoltrate ai Responsabili di FV locali che hanno inserito il caso nella RNF. Questo è il principale motivo per cui ai MAHs è lasciata la visibilità (parziale) dei dati contenuti nella RNF.
Follow-up - GVP VI

Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 102(c) and (e) of Directive 2001/83/EC [DIR Art 107a(1)].

Furthermore, for reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports [DIR Art 107a(2)].
Follow-up - GVP VI

The criteria upon which a MAH may be involved include situations where:

- **important additional information** is necessary for case evaluation or reconciliation,

- clarifications is needed regarding **inconsistent** data within ICSRs,

- there is a need to obtain **further information in the context of** the validation of a signal, the evaluation of a safety issue, the assessment of a PSUR, or the confirmation of a safety concern in a RMP.
Types of Reports

**Unsolicited source**
- Spontaneous
- Literature
- Non-medical sources
- Internet -digital media

**Solicited source**
- Clinical Trials
- Non interventional studies
- Registries
- Named patient use programmes
- Compassionate use
GVP VI: Management of ICSR for non-interventional post-authorisation studies, compassionate use and named patient use

1. System should be in place to record and document complete and comprehensive case information on solicited adverse events.

2. These collected adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medicinal products. A method of causality assessment should be applied for assessing the causal role of the studied (or supplied) medicinal products in the occurrence of the solicited adverse events. An adverse event should be classified as an adverse reaction, if there is at least a reasonable possibility of causal relationship with the product.
Management of ICSR for non-interventional post-authorisation studies, compassionate use and named patient use

3. Reports of adverse reactions, suspected to be related to the studied (or supplied) medicinal product by the primary source or by the notified organisation, should be classified and submitted as solicited report ICSR.

4. Other reports of adverse events should be summarised as part of any interim safety analysis and in the final study report, where applicable.
Management of ICSR for non-interventional post-authorisation studies, compassionate use and named patient use

5. In situations where an adverse reaction is suspected to be related to a medicinal product other than the studied (or supplied) medicine and does not result from a possible interaction with it, the report should be managed, classified and submitted as spontaneous ICSR.

6. It should be notified by the primary source (healthcare professional or consumer) to the competent authority in the Member State where the reaction occurred or to the MAH of the suspected medicinal product, but not to both to avoid duplicate ICSRs submission.
Non-interventional post-authorisation studies with a design based on SECONDARY use of data

• The design of such studies is characterised by secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses.

• For these studies, the submission of suspected adverse reactions in the form of ICSRs is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification.
Emerging Safety Issue

- A safety issue considered by a marketing authorisation holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients’ or public health and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

- An ESI is in addition to the ICSR submission requirements, when the emerging safety issue refers to a single case of suspected adverse reactions.
Emerging Safety Issue

Examples include:

- major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;

- major safety issues identified through the spontaneous reporting system or publications in the scientific literature, which may lead to considering a contraindication, a restriction of use of a medicinal product or its withdrawal from the market;

- major safety-related regulatory actions outside the EU, e.g. a restriction of use of a medicinal product or its suspension.
Emerging Safety Issue

• When the MAH in the EU becomes aware of an emerging safety issue from any source, they should notify it in writing to the competent authority(ies) of Member State(s) where the medicinal product is authorised and to the Agency to the mailbox P-PV-emerging-safety-issue@ema.europa.eu”.

• This should be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

• For AIFA: esi@aifa.gov.it
Emerging Safety Issue

MAH

as soon as possible and no later than 3 working days

- Agency to the mailbox
  P-PV-emerging-safety-issue@ema.europa.eu

- Competent authority(ies) of MSs where the medicinal product is authorised
  (AIFA to the mailbox esi@aifa.gov.it)
Emerging Safety Issue

• When notifying an emerging safety issue, the marketing authorisation holder should describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and should provide any relevant documentation available at the time of initial notification.

• Upon being notified of an emerging safety issue, the national competent authorities and/or the Agency as appropriate should promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised. This may involve the consultation of the Incident Review Network, if warranted.
Emerging Safety Issue and possible actions

Should the MAH decide as a result of the emerging safety issue to take any of the following actions:

- temporary or permanent cessation or suspension of marketing of a medicinal product,
- withdrawal of a medicinal product from the market,
- request for the withdrawal of a marketing authorisation
- or non-application for the renewal of a marketing authorisation,
Emerging Safety Issue – GVP IX

In order to ensure its effectiveness, the system should not be saturated by the transmission of less urgent information.

MAHs should only communicate as emerging safety issues those safety concerns which meet the definition
Stand-alone signal notification

When a marketing authorisation holder, based on their assessment of a signal detected through EudraVigilance monitoring, and which does not meet the conditions of ESI, concludes that further analysis of the signal by the competent authorities is required, they should complete the stand-alone signal notification form available on the European medicines web-portal and send it to the Agency using the mailbox MAH-EV-signals@ema.europa.eu and to the competent authorities in Member States where the medicinal product is authorised.

This should be done as soon as possible and no later than 30 days after the marketing authorisation holder has completed their assessment and concluded that further analysis by the competent authorities is required.
Stand-alone signal notification

MAH

*as soon as possible and no later than 30 days*

- Agency to the mailbox
  MAH-EV-signals@ema.europa.eu

- Competent authority(ies) of MSs where the medicinal product is authorised
  (AIFA to the mailbox segnaliFV@aifa.gov.it)
Standalone signal notification

- Within 30 days of receipt of a signal validated by the Agency or a Member State, or a standalone signal notification from a marketing authorisation holder, the PRAC rapporteur or (lead) Member State, as applicable, should confirm or not the signal.
Modifiche all’infrastruttura IT
(Rete Nazionale di Farmacovigilanza - RNF)
Nuovo formato elettronico delle segnalazioni a Eudravigilance

- Le segnalazioni di sospette reazioni avverse saranno registrate in Eudravigilance nel formato elettronico ICH E2B(R3).

- Le autorità competenti nazionali e i titolari di autorizzazione all'immissione in commercio potranno continuare a inviare le segnalazioni nel formato ICH E2B(R2), ma dovranno assicurare che i propri sistemi informatici siano in grado di processare gli E2B(R3) files. Questo potrà essere realizzato sia implementando il nuovo formato nei propri database di farmacovigilanza o attraverso l'implementazione di uno strumento di conversione dei files da E2B(R3) a E2B(R2).
Rete Nazionale di FV - RNF

- Formato ICH E2B(R2)
- Convertitore da E2B(R3) a E2B(R2)
- Modifica visibilità dati da parte dei MAHs
- Modifiche ai campi del formato ICH E2B (R2)
- I Master cases da EV non saranno ricevuti/gestiti
- Re-routing ogni 24 h (per i casi con errore si procederà manualmente)

Le modifiche alla RNF entreranno in produzione il 22 Novembre 2017
MAHs e livello di accesso alla RNF

- Livello di accesso sarà per sostanza attiva di cui hanno almeno un medicinale autorizzato

- Non potranno più inserire o modificare o annullare segnalazioni ad eccezione di ciò che è stato inserito fino al 21/11/2017 che potrà essere modificato o annullato fino al 31/12/2017

- Ridotta visibilità di campi
Attive fino al 31/12/2017 per dare la possibilità di aggiornare le schede inserite dai MAH al 21/11/2017
## RNF e visibilità CRFV

### Gestione Schede
- Inserimento
- Aggiornamento
- Annullamento
- Inserimento tramite XML

### Documentazione
- Workshop Marzo 2002
- Corso Autoapprendimento Corso Autoapprendimento (Pandemia)
- Corso Centri Regionali 2012
- Guida Responsabili FV - Febbraio 2015
- Diapositive Corso Responsabili FV - Giugno 2013
- Documentazione MedDRA

### Visualizzazione
- Singola Scheda
- Lista Schede
- Monitoraggio Attività
- Osservazioni sul caso
- Schede con Osservazioni
- Elenco Modifiche
- Monitoraggio Intensivo

### Dati di Sintesi
- Segnalazioni per Fonte
- Segnalazioni per Anno/Regione
- Segnalazioni per SOC/ART
- Segnalazioni per Sesso/Eta
- Segnalazioni per ATC
- Segnalazioni per PA/SM
- Segnalazioni per Anno/Eta

### Utilità
- Rubrica
- Modifica Dati Personal
- Dizionari
- Richiesta Elaborazione
- Report Elaborazione

### Richiesta Profilo
- Richiesta nuovo profilo
RNF e schede da Eudravigilance

- Le segnalazioni provenienti da Eudravigilance non potranno essere aggiornate o eliminate; il sistema segnalerà che l’operazione non è autorizzata.
RNF e codici delle schede

• All’interno della RNF tutte le segnalazioni conterranno il codice della RNF e per quelle provenienti da Eudravigilance sarà presente anche il codice di Eudravigilance corrispondente World Wide Unique Case Identification Number (WWID)

• Le schede potranno essere ricercate sia per Codice RNF che per Codice EV WWID
Types of Reports

Unsolicited source:
- Spontaneous
- Literature
- Non-medical sources
- Internet - digital media

Solicited source:
- Clinical Trials
- Non interventional studies
- Registries
- Named patient use programmes
- Compassionate use
RNF e tipo segnalazione

• Le segnalazioni dovranno essere obbligatoriamente categorizzate per tipo di segnalazione.

• A livello di caso dovrà quindi essere compilato il campo “tipo segnalazione” scegliendo il valore dal seguente menu a tendina:

1. Spontanea
2. Da studio
   a) Da studio non interventistico
   b) Da usi individuali (uso compassionevole, named patient basis)
3. Altro
4. Informazione non disponibile al sender
RNF e iniziali paziente

- Le Iniziali del paziente saranno visualizzate come unica stringa senza distinzione fra Nome e Cognome.
Sezione Sintesi del caso (ex Follow up)

- La sezione attualmente denominata “Follow-up” sarà rinominata in “Sintesi del caso”

- Il campo di testo libero attualmente presente sarà organizzato in tre campi di testo libero e precisamente:
  - Descrizione del caso
  - Commento del segnalatore
  - Commento del sender

- L’intera sezione non sarà visibile ai MAH
Allegati in RNF

• Fino a quando le schede in RNF saranno nel formato ICH E2B(R2) gli allegati non saranno trasmessi ad Eudravigilance
Raccomandazioni per l’inserimento dei casi italiani in EV

Ove possibile si raccomanda per le segnalazioni con **Country Italy** di compilare il campo **State** riportando la **Regione** di appartenenza del segnalatore.
Training

• The Agency is supporting national competent authorities (NCAs) and marketing authorisation holders (MAHs) in the European Economic Area (EEA) through targeted e-learning and face-to-face trainings, webinars and information days.
EMA strongly recommends that both new and existing users complete all EudraVigilance and pharmacovigilance trainings recommended for their stakeholder group, as both the EudraVigilance system and pharmacovigilance guidelines are subject to updates.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb
Documenti AI FA che saranno oggetto di modifica

- FAQ AI FA
- Linee Guida per i Responsabili di FV
- Linee Guida Per i Centri Regionali di FV
- Linea Guida sugli Studi Osservazionali

Sezioni Portale AI FA che saranno oggetto di modifica

- La legislazione di farmacovigilanza
- Modalità di segnalazione
- Come funziona la Rete Nazionale di Farmacovigilanza
- Eudravigilance
Principali riferimenti utili

1. Revised EudraVigilance stakeholder change management plan (23 June 2017 - EMA/325783/2016 Revision 2 Corr*)

2. European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (16 December 2016 - EMA/759287/2009 Revision 3*)


5. GVP module IX - rev 1

6. GVP module VI - rev 2
Grazie dell’attenzione