FV SIGNÁLY – JAK S NIMI PRACOVAT

MUDr. Jana Šípková

Obsah prezentace

- Obecné principy signal managementu
- Monitoring EudraVigilance
- Schematické shrnutí postupů pro držitele
- Příklady hodnocení bezpečnostních dat z praxe

Obecné principy signal managementu

Signal management

GVP Module IX Signal management (Rev 1)

9/10/2017

Signal management na stránkách EMA:

www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

Signal management

A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation. The European Medicines Agency (EMA), together with the regulatory authorities in the Member States and marketing authorisation holders are responsible for detecting and managing safety signals.

Safety signals can be detected from a **wide range of sources**, such as spontaneous reports, clinical studies and scientific literature. The EudraVigilance database is an important source of information on suspected adverse reactions and signals.

The presence of a safety signal does not directly mean that a medicine has caused the reported adverse event. An illness or another medicine taken by the patient could also be the cause.

The assessment of safety signals establishes whether or not there is a **causal relationship** between the medicine and the reported adverse event.

The evaluation of safety signals is part of routine pharmacovigilance and is essential to ensuring that regulatory authorities have the most up-to-date information on a **medicine's benefits and risks**.

Monitoring EudraVigilance: legal basis and guidance (revised 09/01/2018)

Commission Implementing Regulation (EU) No 520/2012 (article 18) requires EMA, national competent authorities and marketing authorisation holders (MAHs) to continuously monitor the data available in EudraVigilance.

It also requires MAHs to inform EMA and national competent authorities of validated signals detected when monitoring the database.

On 22 November 2017, EMA launched the new EudraVigilance system and enabled MAH access to the system.

Guidance on regulatory requirements and on the monitoring and reporting processes for signals is available in good pharmacovigilance practices (GVP) Module IX on signal management.

In line with GVP IX requirements, **standalone notifications of signals** detected in EudraVigilance should be sent to the Agency (MAH-EV-signals@ema.europa.eu) and to

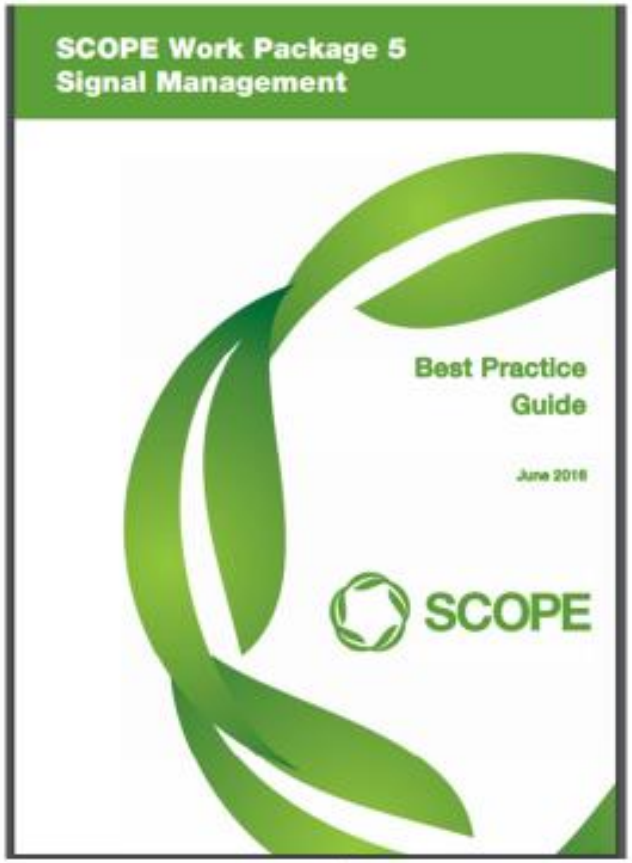
Další užitečné zdroje informací:

- *SCOPE work package 5 – Signal management Best Practice guide*
- ✓ www.scopejointaction.eu

- *EMA Questions and Answers on Signal Management*
- ✓ *http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150743.pdf*

- *Screening for Adverse Reactions in EudraVigilance*
- ✓ *www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf*

- *Report of CIOMS Working group VIII on Practical aspects of signal detection in Pharmacovigilance*



Best practice guide

Example

The EMA 2015 Annual Report on EudraVigilance (12) shows that the PRAC prioritised and assessed 102 signals during 2015. 33% of the signals resulted in a recommendation for an update of the product information (PI), including the distribution of a Direct Healthcare Professional Communication (DHPC) on four occasions to highlight important new safety information to healthcare professionals. Twenty-seven signals (26%) were closed and subject to routine safety monitoring. Four signals resulted in a recommendation to update the RMP; another signal was further assessed through a Post Authorisation Safety Study (PASS), and one signal was evaluated in a referral procedure. The evaluation of 35 signals (35%) was ongoing, including 20 via a follow-up signal procedure and 15 in the next PSUR.

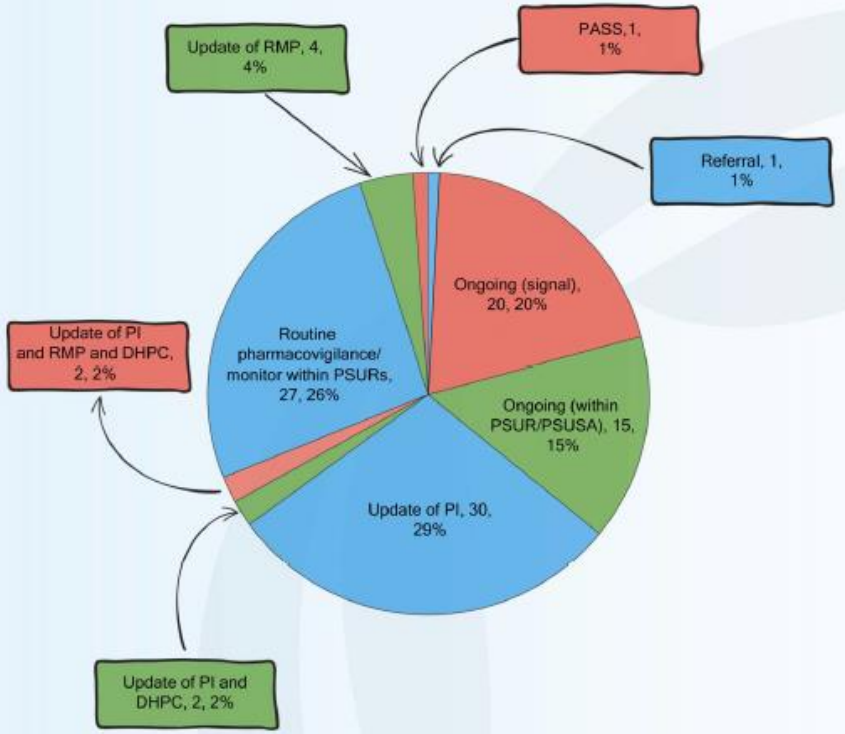
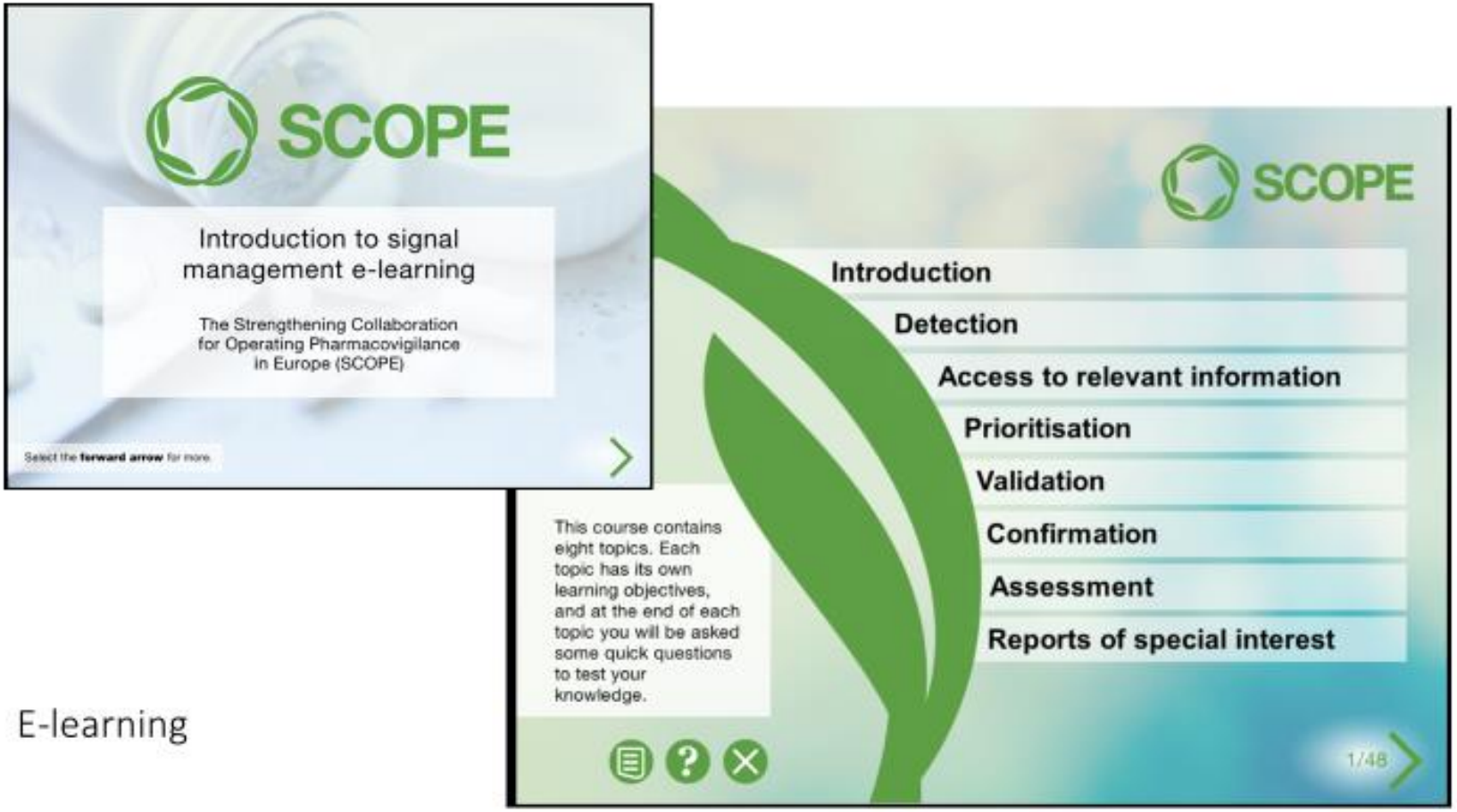


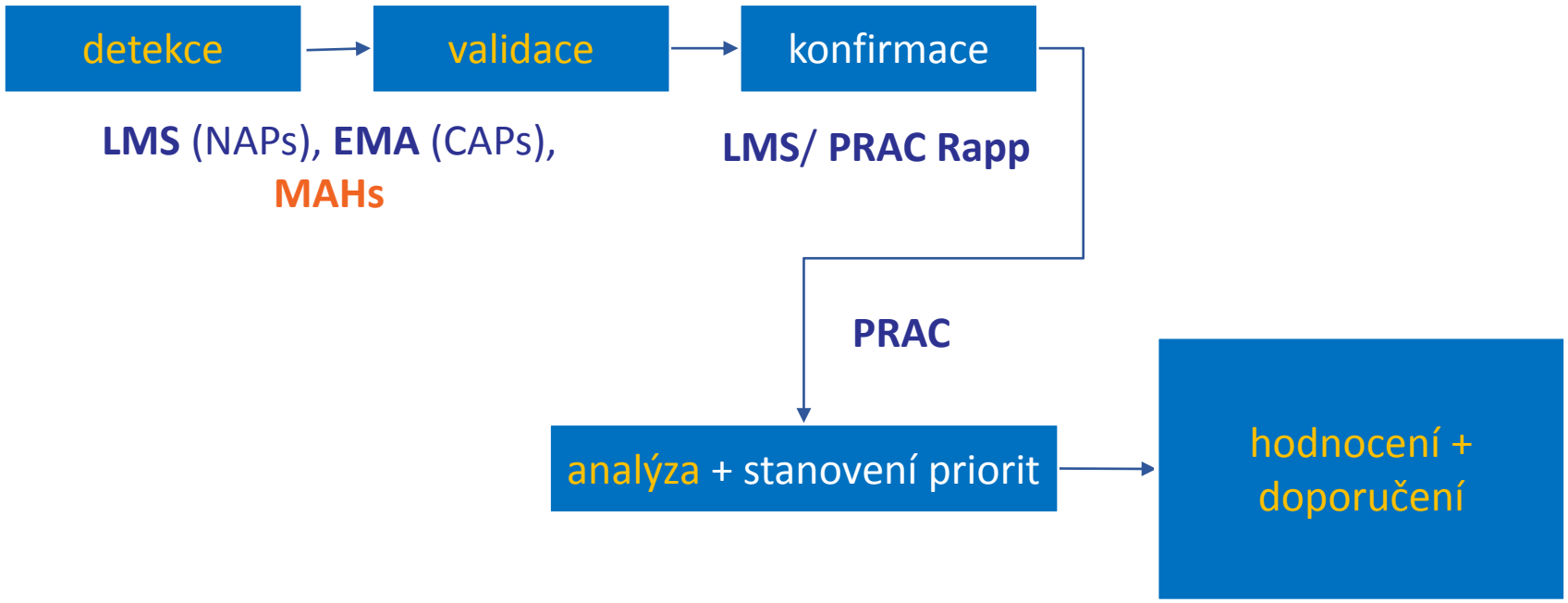
Figure 1. Outcomes of PRAC signal assessments in 2015

EMA 2015 Annual Report on EudraVigilance (12)



E-learning

Signal management process



Aktuální přehled lead member states

List of substances and products subject to work-sharing for signal management

(3/2018, CZ je lead member state pro 66 látek)

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/04/WC500226389.xlsx

Member State signal management work-sharing

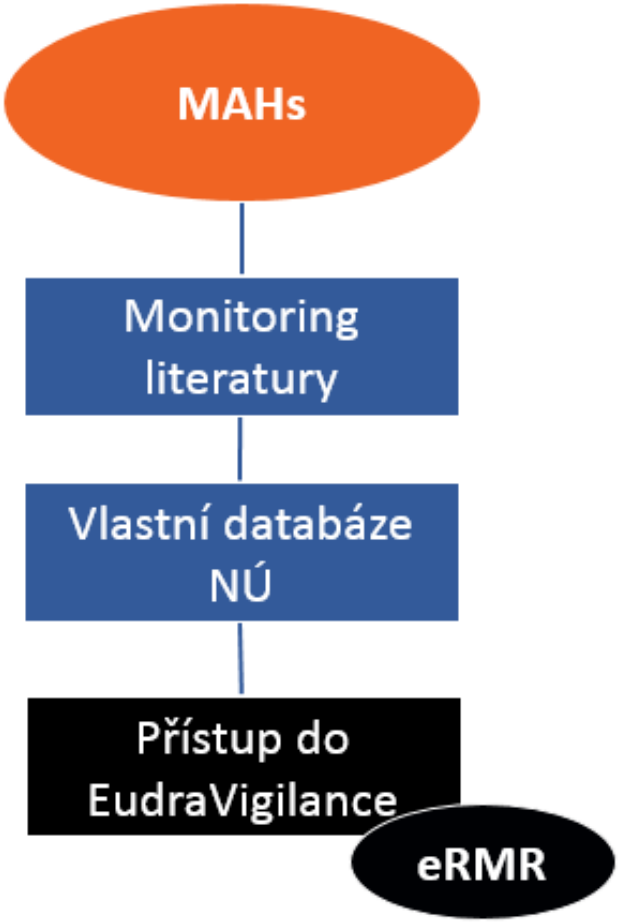
A **lead Member State** may be appointed to monitor data in EudraVigilance, validate and confirm signals on behalf of the other Member States. This applies to active substances contained in medicinal products authorised nationally in more than one Member State.

▸ List of substances and products subject to worksharing for signal management (last updated 08/03/2018)

For substances with no lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised.

Names of active substances or medicinal products	Lead Member Sta
acetic acid glacial / calcium chloride dihydrate / glucose monohydrate / magnesium chloride hexahydrate / potassium chloride / sodium chloride / sodium dihydrogen phosphate	Czech Republic
alprostadil	Czech Republic
amlodipine / candesartan	Czech Republic
bendroflumethiazide	Czech Republic
bendroflumethiazide / potassium chloride	Czech Republic
benzododecinium bromide	Czech Republic
bismuth subgallate / charcoal activated / citric acid	Czech Republic
boric acid / carbethopendecinium bromide / sodium tetraborate	Czech Republic
bromelain	Czech Republic
brompheniramine	Czech Republic
caffeine / paracetamol	Czech Republic
carbaethopendecinium	Czech Republic
carbaethopendecinium bromide / trimecaine hydrochloride	Czech Republic
carboprost	Czech Republic
cefixime	Czech Republic
cetylpyridinium	Czech Republic
charcoal activated / sodium thiosulfate	Czech Republic
chlorambucil	Czech Republic
chloramphenicol	Czech Republic
chloroxine	Czech Republic
chlorphenoxamine hydrochloride	Czech Republic
chorionic gonadotrophin	Czech Republic
citrulline malate	Czech Republic
clomifene	Czech Republic

Signal worksharing



QPPV obdrží v týdnu před jednáním PRACu seznam konfirmovaných a nekonfirmovaných signálů

Konfirmované signály se objeví na agendě PRACu

Držitelé spolupracují s EMA/NCAs a doloží požadovaná data

Zúčastnění držitelé mají možnost připomínkovat hodnotící zprávu a navržené závěry

Všichni držitelé předmětné léčivé látky implementují závěry PRACu

Příklad - PRAC agenda 4/2018

Závěry jednání PRAC

SÚKL

www.sukl.cz/leciva/doporuceni-prac-k-farmakovigilancnim-signalum-2018

EMA

www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp

SÚKL

Doporučení PRAC k farmakovigilančním signálům - 2018

Státní ústav pro kontrolu léčiv informuje držitele rozhodnutí o registraci o zveřejnění nového doporučení PRAC ke zhodnoceným farmakovigilančním signálům, z jehož závěrů vyplývají požadavky na aktualizaci souhrnu údajů o přípravku a příbalové informace.

Datum zveřejnění	Termín implementace	Léčivá látka	Dotčené léčivé přípravky	PRAC recommendation	Český překlad
7.5.2018	2 měsíce	Amitriptylin	AMITRIPTYLINUM LP.xlsx, soubor typu xlsx, (9,84 kB)	PRAC recommendations 9.-12.4.2018.pdf, soubor typu pdf, (102,05 kB)	PRAC doporučení AMITRIPTYLIN.pdf, soubor typu pdf, (84 kB)
3.4.2018	2 měsíce	Norepinefrin	NOREPINEPHRINUM LP.xlsx, soubor typu xlsx, (8,89 kB)	PRAC recommendations 5.-8.3.2018.pdf, soubor typu pdf, (81,33 kB)	PRAC doporučení NOREPINEFRIN.pdf, soubor typu pdf, (1 kB)
5.3.2018	3 měsíce	Ritonavir, lopinavir-ritonavir, ombitasvir-paritaprevir-ritonavir, levothyroxin	RITONAVIRUM LP.xlsx, soubor typu xlsx, (9,91 kB) LEVOTHYROXINUM LP.xlsx, soubor typu xlsx, (11,51 kB)	PRAC recommendations 5.-8.2.2018.pdf, soubor typu pdf, (83,32 kB)	PRAC doporučení RITONAVIR, LOPINA RITONAVIR, OMBITASVIR-PARITAPREVIR-RITONAVIR, LEVOTHYROXIN.pdf soubor typu pdf, (1(kB)
5.3.2018	2 měsíce	Hydroxykarbamid	HYDROXYCARBAMIDUM LP.xlsx, soubor typu xlsx, (8,72 kB)	PRAC recommendations 5.-8.2.2018.pdf, soubor typu pdf, (83,32 kB)	PRAC doporučení HYDROXYKARBAMID soubor typu pdf, (86 kB)

SÚKL

PRAC recommendations on safety signals: monthly overviews

Back to top ▲

Document(s)	Language	Status	First published	Last updated	Effective Date
PRAC recommendations on signals adopted at the 9-12 April 2018 PRAC meeting	(English only)	adopted	07/05/2018		
New product information wording: extracts from PRAC recommendations on signals adopted at the 9-12 April 2018 PRAC	EN = English GO		07/05/2018		
PRAC recommendations on signals adopted at the 5-8 March 2018 PRAC meeting	(English only)	adopted	03/04/2018		
New product information wording: extracts from PRAC recommendations on signals adopted at the 5-8 March 2018 PRAC	EN = English GO		03/04/2018		
PRAC recommendations on signals adopted at the 5-8 February 2018 PRAC meeting	(English only)	adopted	05/03/2018		
New product information wording: extracts from PRAC recommendations on signals adopted at the 5-8 February 2018 PRAC	EN = English GO		05/03/2018		
PRAC recommendations on signals adopted at the PRAC meeting of 8-11 January 2018 meeting	(English only)	adopted	05/02/2018	15/02/2018	
New product information wording: extracts from PRAC recommendations on signals adopted at the 8-11 January 2018 PRAC	EN = English GO		05/02/2018		

Monitoring EudraVigilance

Pilotní projekt

- ✓ Od 22/2/2018 po dobu 1 roku
- ✓ 3 měsíce *„grace period“*
- ➢ nyní povinné průběžné sledování EudraVigilance (EV) pro držitele vybraných léčivých látek (aktualizace 4/2018):

List of active substances involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders

SÚKL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 April 2018
EMA/701527/2017 Corr 5
Inspections, Human Medicines Pharmacovigilance & Committees

List of active substances and combinations involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders

Introduction:

Commission Implementing Regulation (EU) No 520/2012 requires marketing authorisation holders (MAHs) to continuously monitor EudraVigilance data and inform EMA and national competent authorities of validated signals detected in the database. The process and requirements for signals detected by MAHs in EudraVigilance are outlined in the Good Pharmacovigilance Practices (GVP) Module IX on signal management.
For a pilot period starting on 22 February 2018, MAHs will be required to perform signal detection in EudraVigilance and follow the above requirements, **only for active substances and combinations included in the present list.**
For information, the list is based on all active substances and combinations that were included in the list of medicinal products subject to additional monitoring as of 25 October 2017 (Rev. 49). However, all medicinal products containing active substances or combinations included in the present list will be involved in the pilot, regardless of whether or not the medicinal products themselves are subject to additional monitoring. A slash ('/') is used to separate the different active substances contained in a combination. Combinations not mentioned in the list are excluded from the pilot, even if the individual components of the combination are listed. Likewise, if a combination is listed but the individual substances are not listed separately, then those individual substances are excluded from the pilot.
Corrections on 05 April 2018:
Daclizumab, simeprevir and telavancin have been removed from the list as the corresponding medicinal products

Related Information:

Commission Implementing Regulation (EU) No 520/2012
Guideline on good pharmacovigilance practices (GVP) - Module IX - Signal management
Information on signal management

Active substances and combinations of active substances
A/H5N1 pre-pandemic influenza vaccine (whole virion, vero cell derived, inactivated)
Aclidinium bromide
Aclidinium bromide / formoterol fumarate dihydrate
Adalimumab
Afamelanotide
Afatinib
Alanine / arginine / aspartic acid / calcium chloride / cysteine / glucose monohydrate / glutamic acid / glycine / histidine / isoleucine / leucine / lysine monohydrate / magnesium acetate / methionine / olive oil / ornithine hydrochloride / henylalanine / potassium acetate / proline / serine / sodium chloride / sodium glycerophosphate / soybean oil / taurine / threonine / tryptophan / tyrosine / valine
Albiglutide

Stanovení frekvence monitoringu EV

- Frekvence s ohledem na bezpečnostní data, která jsou pro danou látku k dispozici s přihlédnutím k:
- Stáří látky
- Expozici
- Bezpečnostním rizikům v RMP (zejména important potential risks a missing information)
- Frekvenci předkládání PSURů
- Počtům přijatých hlášení
- Specifickému zájmu (např. veřejnost)

- Konkrétní frekvence se stanoví a popíše v interních postupech držitele, data z EV by však měla být monitorována minimálně jednou za 6 měsíců, pro látky spadající pod additional monitoring má být monitoring častější

Užitečné zdroje informací:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb

Home ▸ Human regulatory ▸ Research and development ▸ Pharmacovigilance ▸ EudraVigilance ▸ EudraVigilance training

EudraVigilance training and support

Email Print Help Share

The European Medicines Agency (EMA) offers training to support stakeholders in meeting their pharmacovigilance obligations when using EudraVigilance. Training is important to ensure that users understand its functionalities and submit high quality data which adhere to standards that allow for adequate monitoring of the safety of medicines and the protection of public health in the European Union (EU).

EMA launched a new and improved version of EudraVigilance on 22 November 2017 with enhanced functionalities for reporting and analysing suspected adverse reactions.

The Agency is delivering training courses on the enhanced EudraVigilance system to support national competent authorities (NCAs) and marketing authorisation holders (MAHs) in the European Economic Area (EEA). Training includes 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.

In order to help users prepare for the changes resulting from the enhanced EudraVigilance system, EMA has developed a **modular training curriculum**:

▸ EudraVigilance training plan and curriculum

On this page:

- Face-to-face training
- Support webinars
- Information days
- User guidance
- E-Learning
- Eudravigilance online competency assessment for non-commercial sponsors

www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500219435

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EV-M5b - EVDAS training for Marketing Authorisation Holders

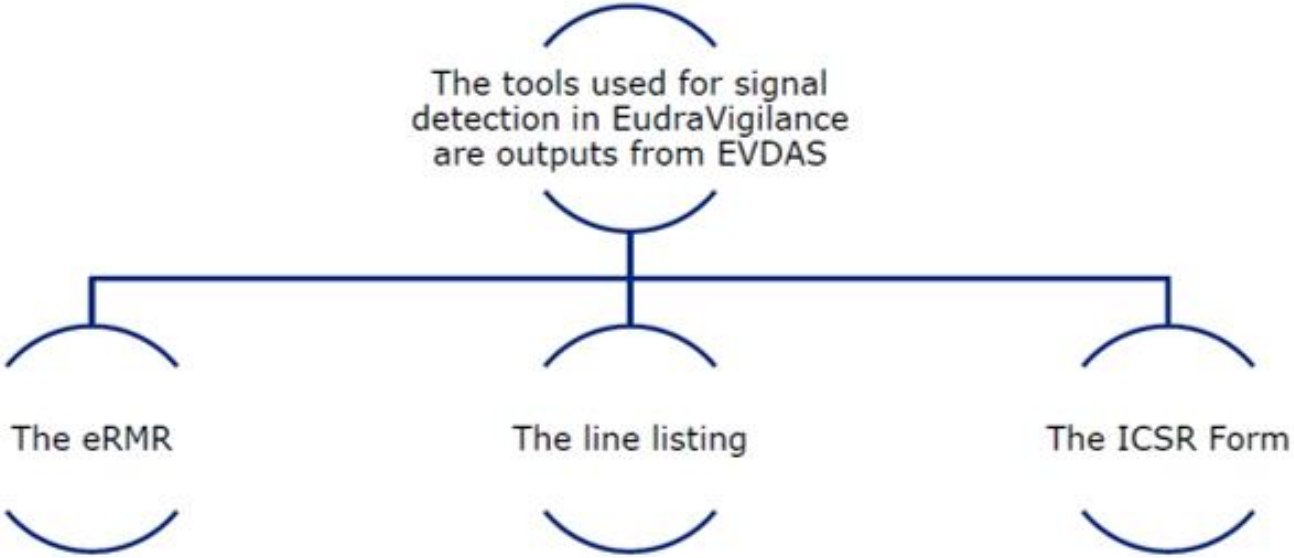
Overview of the EVDAS functionalities and level 1 access to EudraVigilance by Marketing Authorisation Holders to comply with their pharmacovigilance obligations with regards to signal detection and management

Rodrigo Postigo, Signal and Incident Management, Pharmacovigilance and Epidemiology department

An agency of the European Union

EUROPEAN MEDICINES AGENCY

Screening for adverse reactions in EudraVigilance



122 EV-M5b - EVDAS training for Marketing Authorisation Holders

Validace a další hodnocení potenciálního signálu

- **Ověření již známých dat** – SmPC daného přípravku i jiných přípravků s danou LL, informace v RMP, PSUR, probíhajících regulačních procedurách
- **Síla důkazů** – možný biologický či farmakologický mechanizmus, počet případů naznačujících kauzální souvislost (časová souvislost, +de-/rechallenge, chybí jiné vysvětlení obtíží), počet případů vs. expozice, kvalita dostupných dat, vztah dávka-reakce, případně disproporcionalita, počet reakcí v souvislosti s příbuznými termíny

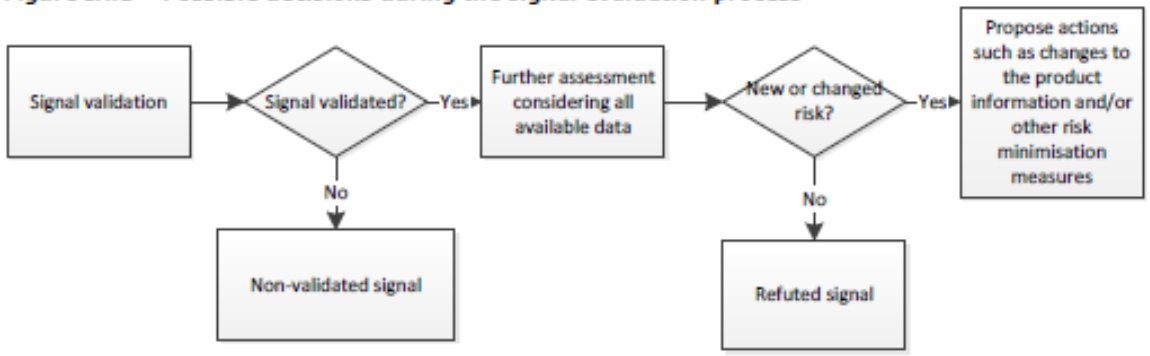
Validace a další hodnocení potenciálního signálu

- **Klinická relevance a kontext** – závažnost reakce, následky a reverzibilita, zvážení možných interakcí, u již známých reakcí zvážení závažnosti, trvání reakce, četnosti výskytu, managementu, reakce u zranitelných populací, reakce v souvislosti s předávkováním, zneužíváním, nesprávným užíváním či off-label použitím

Validace a další hodnocení potenciálního signálu

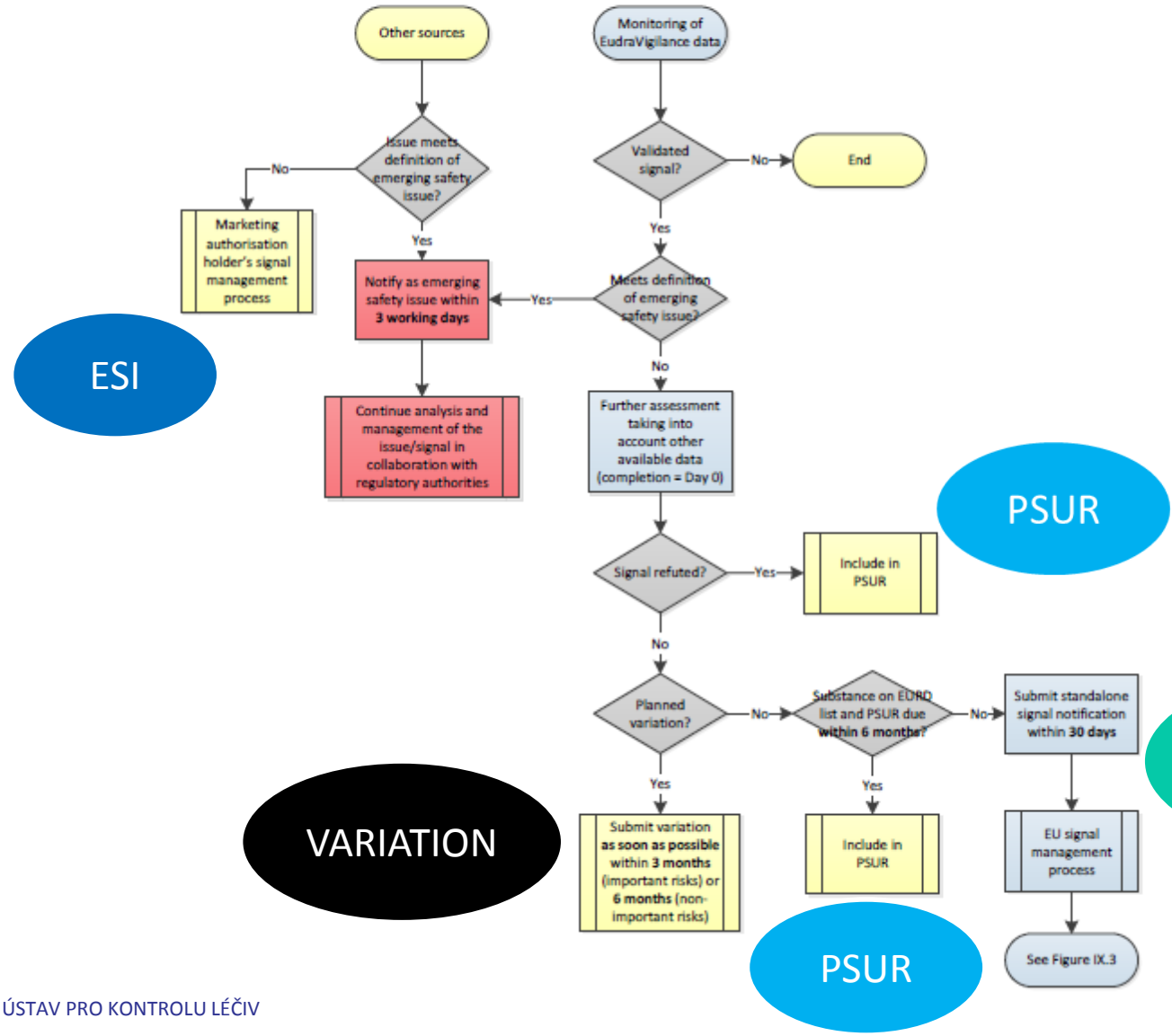
- **Další zdroje dat** - klinické studie, literatura, epidemiologie NÚ či základního onemocnění, preklinická a experimentální data, databáze a informace jiných regulačních autorit

Figure IX.1 – Possible decisions during the signal evaluation process



IX. Appendix 1. Figures on the EU signal management process

Figure IX.2. Notifications and procedural options for emerging safety issues and for signals detected by marketing authorisation holders based on the continuous monitoring of EudraVigilance data



Emerging safety issues (ESI)

p-pv-emerging-safety-issue@ema.europa.eu

- Vyžaduje urgentní pozornost
- Riziko ovlivnění poměru přínosů a rizik přípravku a/nebo riziko pro veřejné zdraví
- Potenciální potřeba promptní komunikace či regulační akce
- Na základě dat ze studií, publikací, spontánních hlášení či regulačních akcí mimo EU (omezení používání či pozastavení registrace)

- Informovat EMA **do 3 pracovních dnů**
- Při stažení přípravku z trhu paralelně informovat withdrawnproducts@ema.europa.eu
- Při problémech s kvalitou přípravku nebo podezření na padělky informovat qdefect@ema.europa.eu

Jak postupovat u validních signálů z EV?

- Momentálně pouze látky z pilotního projektu, pokud vyžadují další analýzu na EU úrovni
- *Standalone signal notification form*
- Vyplněný formulář → EMA: MAH-EV-signals@ema.europa.eu a NCAs, kde je přípravek registrován
- Kontaktní údaje NCAs: *National contact points for standalone signal notifications*
- Předmět e-mailu: *EV signal from <MAH> on <active substance> and <adverse reaction>*

Monitoring EudraVigilance: legal basis and guidance (revised 09/01/2018)

Commission Implementing Regulation (EU) No 520/2012 (article 18) requires EMA, national competent authorities and marketing authorisation holders (MAHs) to continuously monitor the data available in EudraVigilance.

It also requires MAHs to inform EMA and national competent authorities of validated signals detected when monitoring the database.

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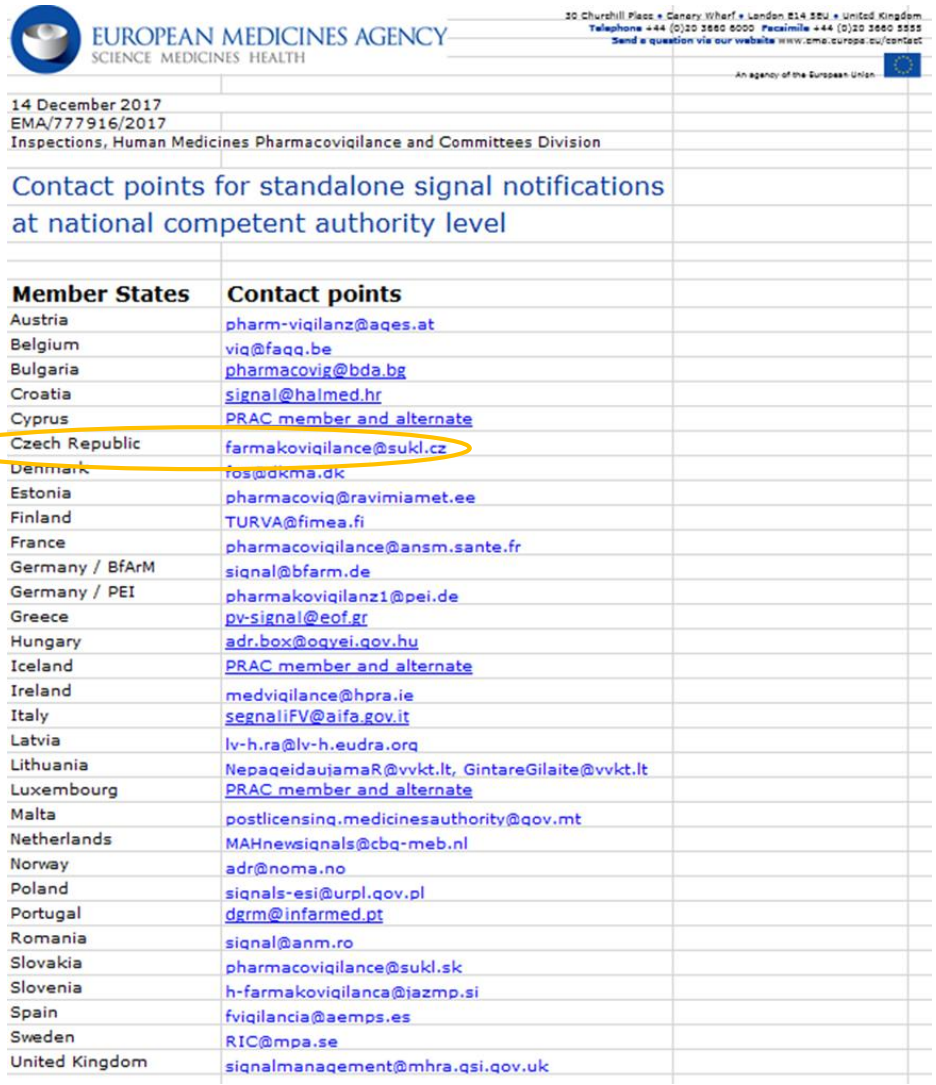
Guidance on regulatory requirements and on the monitoring and reporting processes for signals is available in good pharmacovigilance practices (GVP) Module IX on signal management.

In line with GVP IX requirements, **standalone notifications of signals** detected in EudraVigilance should be sent to the Agency (MAH-EV-signals@ema.europa.eu) and to the competent authorities in Member States where the medicinal product is authorised using the standalone signal notification form (see also transitional arrangements for MAHs).

- National contact points for standalone signal notifications
- Standalone signal notification form

Guidance on the notification of **emerging safety issues** can be found on the EMA's contact page.

EMA has also published **scientific guidance** on routine signal detection methods in EudraVigilance for use by the Agency, national competent authorities and MAHs. The guidance discusses the methods recommended and implemented in EudraVigilance for screening for adverse reactions. It updates and supersedes the previous guideline on the use of statistical signal detection in EudraVigilance.



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SCIENCE MEDICINES HEALTH

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

An agency of the European Union

14 December 2017
EMA/777916/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Contact points for standalone signal notifications at national competent authority level

Member States	Contact points
Austria	pharm-vigilanz@ages.at
Belgium	vig@fagg.be
Bulgaria	pharmacovig@bda.bg
Croatia	signal@halmed.hr
Cyprus	PRAC member and alternate
Czech Republic	farmakovigilance@sukl.cz
Denmark	fos@dkma.dk
Estonia	pharmacovig@ravimiamet.ee
Finland	TURVA@fimea.fi
France	pharmacovigilance@ansm.sante.fr
Germany / BfArM	signal@bfarm.de
Germany / PEI	pharmakovigilanz1@pei.de
Greece	pv-signal@eof.gr
Hungary	adr.box@ogyei.gov.hu
Iceland	PRAC member and alternate
Ireland	medvigilance@hpra.ie
Italy	segnaliFV@aifa.gov.it
Latvia	lv-h.ra@lv-h.eudra.org
Lithuania	NepageidaujamaR@vvkt.lt, GintareGilaite@vvkt.lt
Luxembourg	PRAC member and alternate
Malta	postlicensing.medicinesauthority@gov.mt
Netherlands	MAHnewsignals@cbg-meb.nl
Norway	adr@noma.no
Poland	signals-esi@urpl.gov.pl
Portugal	dgrm@infarmed.pt
Romania	signal@anm.ro
Slovakia	pharmacovigilance@sukl.sk
Slovenia	h-farmakovigilanca@jazmp.si
Spain	fvigilancia@aemps.es
Sweden	RIC@mpa.se
United Kingdom	signalmanagement@mhra.gsi.gov.uk

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/150823/2017

Standalone Signal Notification for <Active substance/INN – BRANDNAME (therapeutic class) and adverse reaction (MedDRA term)>

General guidance

This form should only be used by marketing authorisation holders to notify signals detected in the EudraVigilance database for which they conclude after validation and assessment, that further analysis by the EU regulatory authorities is required.

For a pilot period starting on 22 February 2018, this form should only be used for signals concerning active substances and combinations included in the 'List of active substances involved in the pilot on signal detection in EudraVigilance by MAHs'.

The requirements outlined in the Good Pharmacovigilance Practices (GVP) Module IX on Signal Management (Revision 1) must be followed when completing the form.

Standalone signal notifications should not be used for:

- non-validated or refuted signals,

- signals not detected from the monitoring of EudraVigilance data,

- signals to be included within PSURs or variation applications provided that the conditions outlined in section IX.C.4. of the module are met,

- signals meeting the definition of an emerging safety issue (unless a standalone signal notification is requested by the regulatory authorities).

Once completed, please send the form (in Microsoft Word 2010 format) and any attachments in a single e-mail to the Agency (MAH-EV-signals@ema.europa.eu) and to the competent authorities in Member States where the medicinal product is authorised (see national contact points on the Agency's Signal Management webpage). Please use as e-mail message subject the following format: EV signal from <MAH> on <active substance> and <adverse reaction>.

All the sections should be completed with the information requested or a justification should be provided. Sections should not be left blank.

1. ADMINISTRATIVE INFORMATION

Date of this notification	DD month YYYY
Active substance(s) (invented name(s))	<Text>
Pharmaceutical form(s)/Route(s) of administration / Strength(s)	<Text>
Marketing authorisation holder(s)	<Name(s)>
QPPV	<Name(s) and contact details>
MAH contact person for the signal	<Name(s) and contact details>

Authorisation procedure and number *[Tick the appropriate box(es) below and complete as appropriate.]*

- ☐ Centralised: <EMEA/H/C/...>
- ☐ Mutual recognition or decentralised: <XX/H/...>
- ☐ National: <marketing authorisation number(s)>

Member State(s) in which the MAH holds a marketing authorisation for the medicinal product(s) *[Tick the appropriate box(es) below.]*

<Only applicable for non-centrally authorised products>

☐ AT	☐ BE	☐ BG	☐ CY	☐ CZ	☐ DE	☐ DK	☐ EE
☐ ES	☐ FI	☐ FR	☐ GR	☐ HR	☐ HU	☐ IE	☐ IS
☐ IT	☐ LI	☐ LT	☐ LU	☐ LV	☐ MT	☐ NL	☐ NO
☐ PL	☐ PT	☐ RO	☐ SE	☐ SI	☐ SK	☐ UK	

Marketing authorisation legal basis *[Tick the appropriate box(es) below.]*

<As outlined in Directive No 2001/83/EC>

- ☐ Article 8(3) - Full application
- ☐ Article 10(1) - Generic application
- ☐ Article 10(3) - Hybrid application
- ☐ Article 10(4) - Similar biological application
- ☐ Article 10a - Well-established use application
- ☐ Article 10b - Fixed combination application
- ☐ Article 10c - Informed consent application
- ☐ Other – Please specify: <Text>

Next PSUR submission date *[if PSURs are required for the medicinal product]*	<DD month YYYY> ☐ PSUR not required.

2. SIGNAL DESCRIPTION

2.1. Highlights

Clinical relevance: <Text>

<Please briefly summarise how seriousness criteria were met in the cases, e.g. fatal, life-threatening, hospitalisation etc. See GVP Module VI.A.1.6.>

Relevant statistical measures: <Text>

<Please provide the relevant ROR values (in particular the lower bound of the 95% confidence interval) from EudraVigilance, as well as any other relevant statistical measures if applicable.>

Patient exposure: <Text>

<Please provide the most recent estimate of the population cumulatively exposed to the medicinal product in the post-authorisation setting and in clinical trials if applicable. Methods used to calculate the exposure do not need to be included>.

Previous awareness: <Text>

<Please provide information on any regulatory actions or previous assessments, performed at national, EU or non-EU level in relation to the signal. Please ensure, wherever possible, that the signal is not already addressed in other EU SPCs for the active substance, or considered by EMA/PRAC.>

Additional sources other than EudraVigilance:

☐ Literature ☐ MAH database

☐ Clinical trials ☐ Other *[please specify below]*

2.2. Background

<Text here.>

<This section should include a concise summary of the relevant information on the product(s)/ active substance (including therapeutic indication(s)), and on the adverse reaction(s) (e.g. morbidity, epidemiology, case definition, etc.)>

2.3. Signal validation and further assessment

2.3.1. Evidence from EudraVigilance

Date of the query: <DD month YYYY> Monitoring periodicity: <Text here.>

<Text here.>

<This section should include a summary of evidence from EudraVigilance, highlighting the strength of evidence, clinical relevance and a summary of the supportive cases. MedDRA terms used, number of cases, positive de-challenge or re-challenge, seriousness, dose-reaction relationship, biological and temporal plausibility, causality assessment, clinical context (e.g. drug interactions, specific population, risk factors) and quality of documentation should be provided.>

2.3.2. Evidence from other sources

<Text here.>

<This section should include a summary of all additional evidence, e.g. from the MAH database, scientific literature, clinical trials…>

3. CONCLUSION

<Text here.>

<This section should include a brief statement highlighting why further analysis by the EU regulatory authorities is warranted and proposed actions>.

4. ANNEXES

<Text here.>

<List of literature references, if applicable>

<List of attachments, if applicable>

Schematické shrnutí postupů pro držitele

IX. Appendix 1. Figures on the EU signal management process

Figure IX.2. Notifications and procedural options for emerging safety issues and for signals detected by marketing authorisation holders based on the continuous monitoring of EudraVigilance data

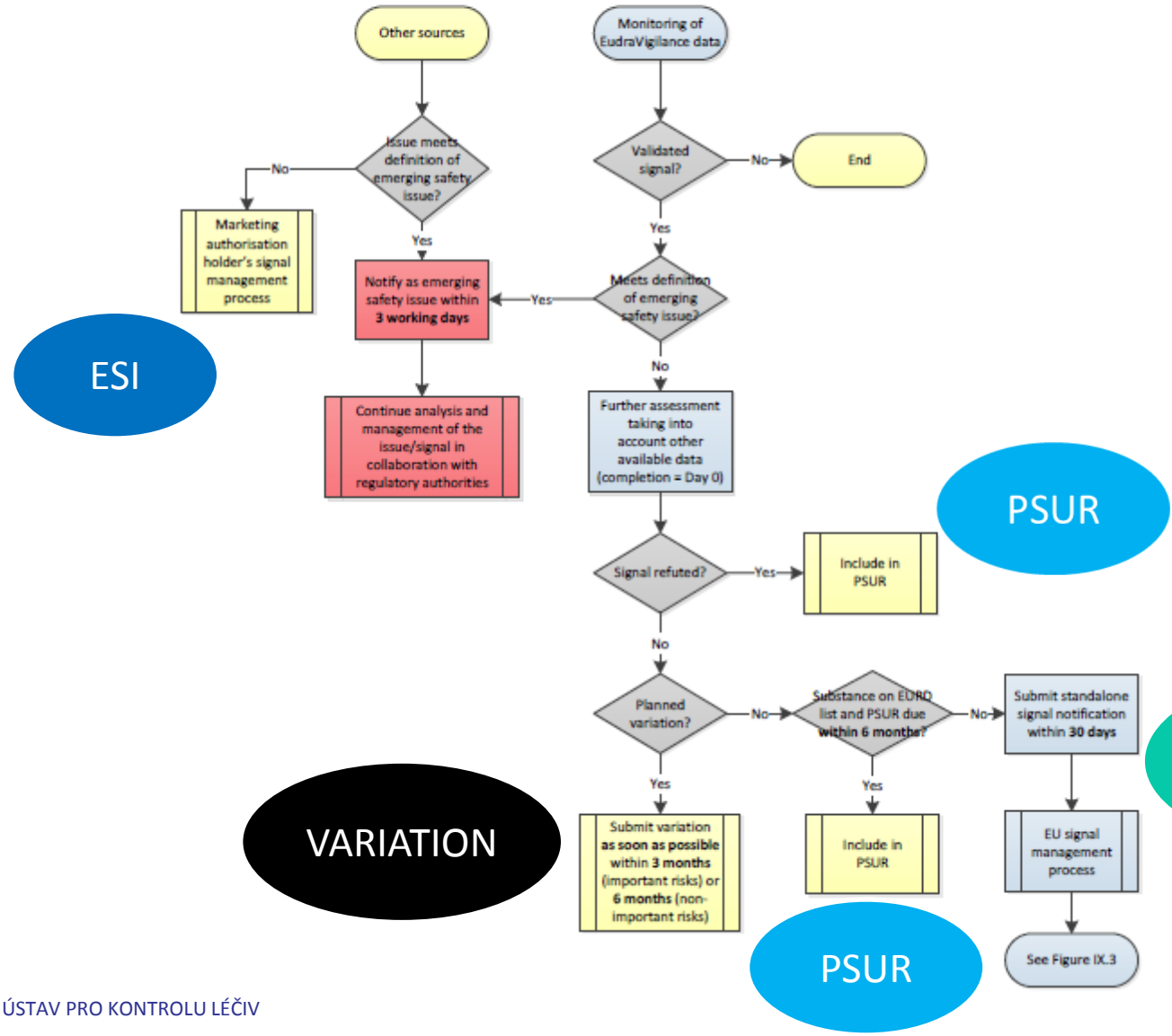


Figure IX.3. Confirmation process for standalone signal notifications from marketing authorisation holders

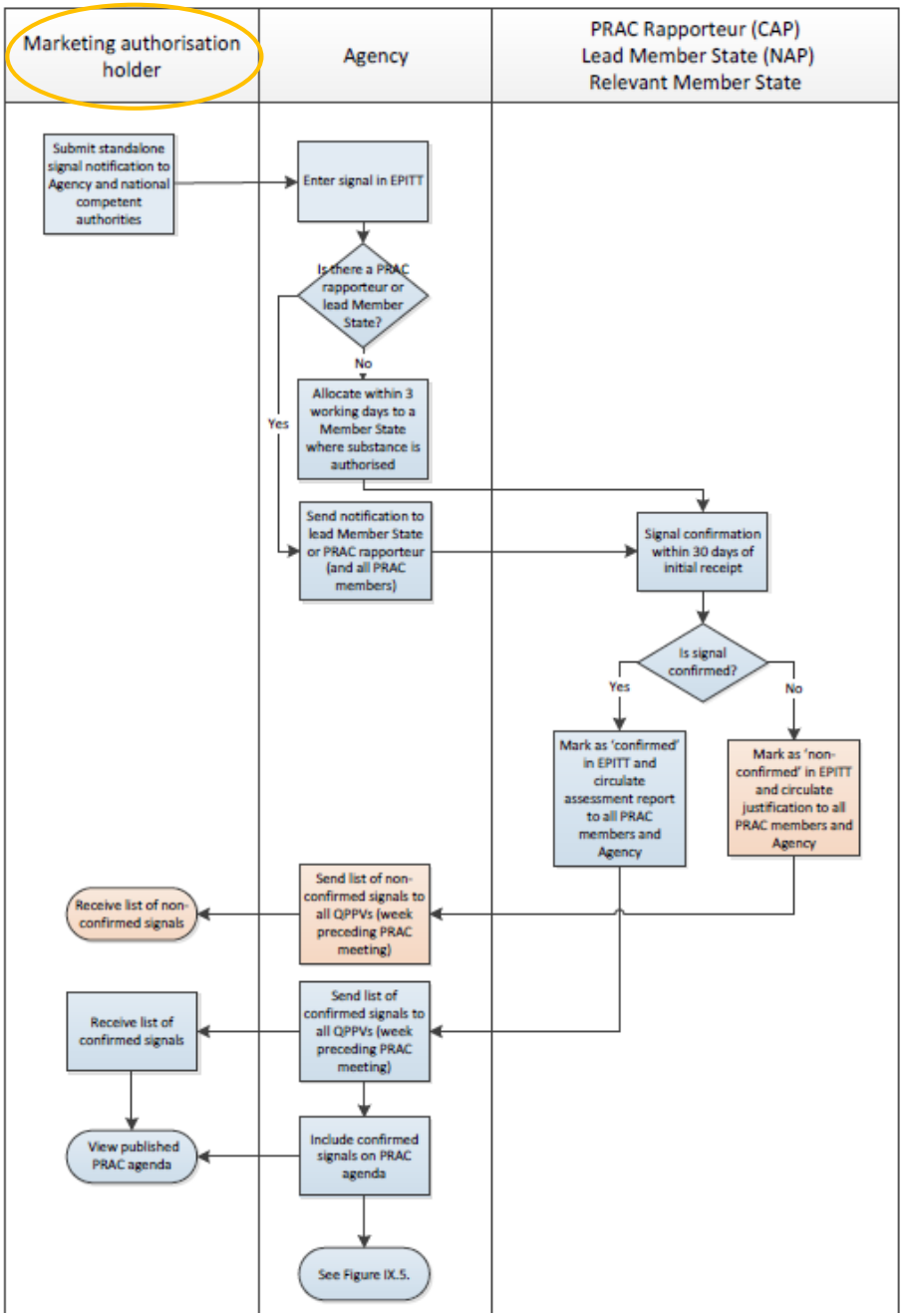


Figure IX.5. Process for analysis, prioritisation and assessment of signals by the PRAC

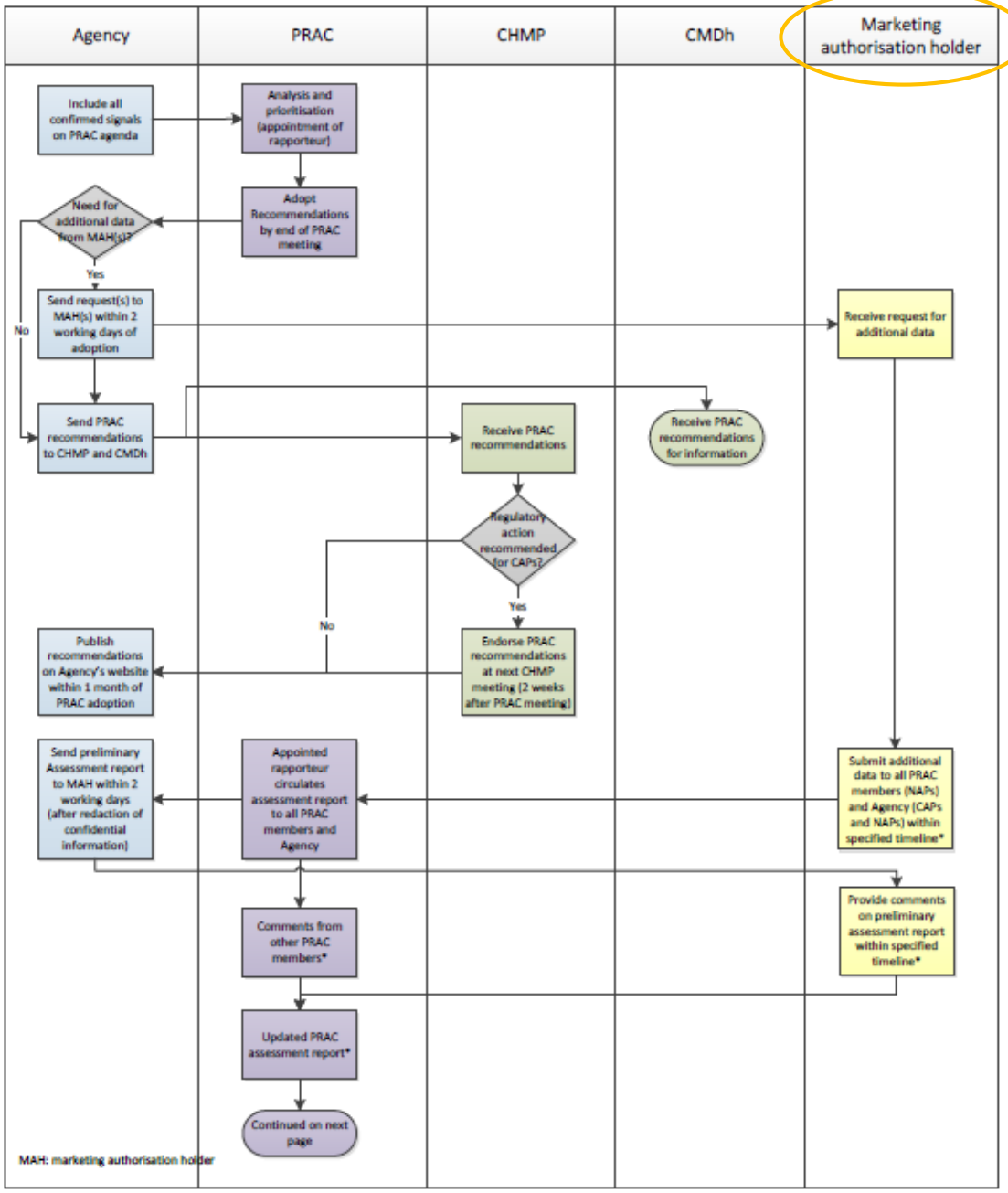
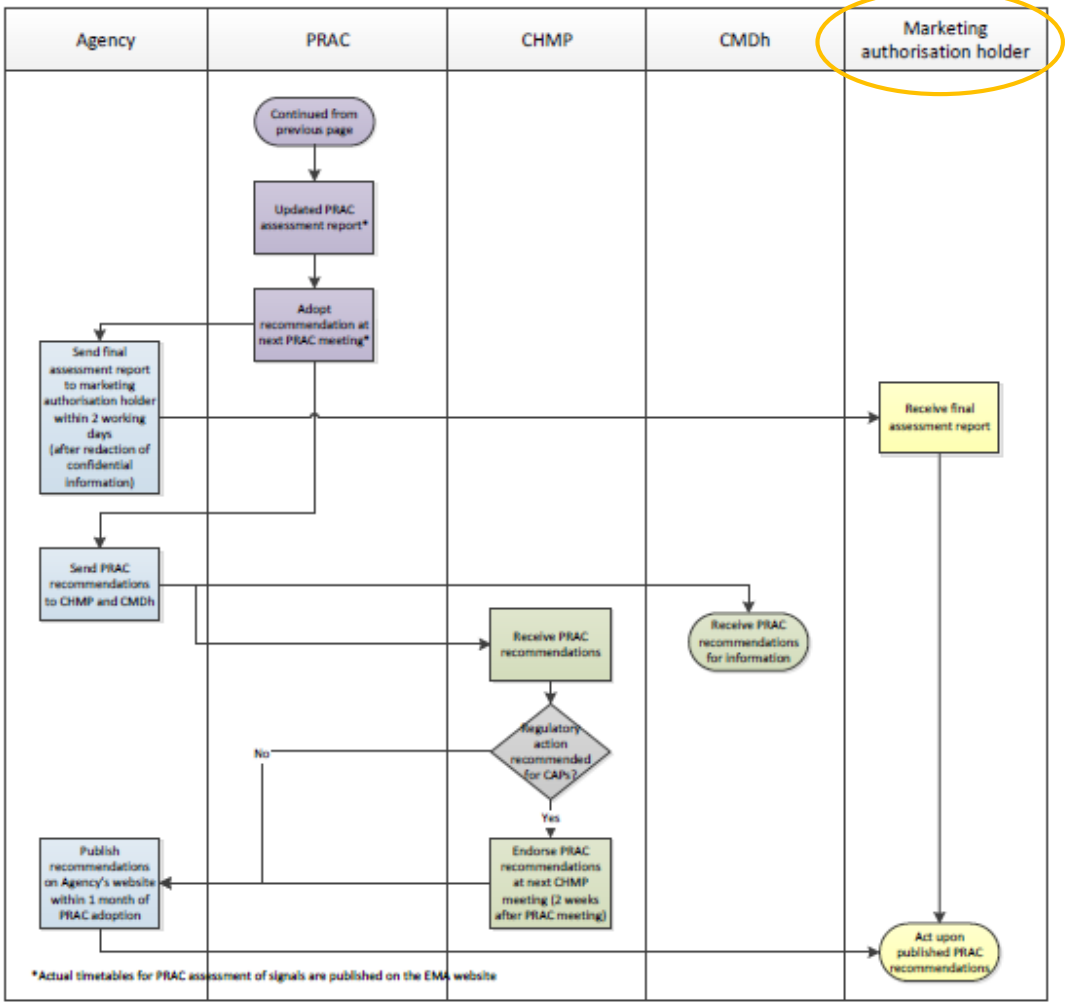


Figure IX.5. (continued) Process for analysis, prioritisation and assessment of signals by the PRAC



Příklady hodnocení bezpečnostních dat z praxe

Ulipristal acetát

- Indikovaný k léčbě děložních myomů
- 9/2017 - na základě signálu – 4 případy závažného jaterního poškození, z toho ve 3 případech nutná transplantace jater
- 12/2017 – na základě zhodnocení možné kauzální souvislosti - zahájení referralu
- 2/2018 – předběžná doporučení – nezahajovat léčbu u nových pacientek ani další léčebné cykly u stávajících pacientek, nutné kontroly jaterních funkcí a poučení pacientek o možných příznacích jaterního postižení

Levonorgestrel (IUD)

- 1/2017 - signál úzkosti, panických atak, změn nálad, poruch spánku a neklidu (nervozity)
- Na podkladě petice německé pacientské organizace
- 10/2017 – uzavření hodnocení

Summary of Product Characteristics

Section 4.8

Depressed mood, Depression*

***In the post-marketing cases, anxiety was frequently co-reported with depression**

Package Leaflet

Section 4

Depressed mood, Depression **(which may occur for the first time or worsen if already present, and may include symptoms of agitation and problems with sleep, and may be comorbid with anxiety)**

Daclizumab

- terapie relabujících forem roztroušené sklerózy
- 6/2017 – zahájení referralu Art.20 - fatální případ fulminantního jaterního selhání při dodržení stanovených RMM
- 7/2017 – DHPC - omezení indikace, KI a upozornění do textů
- 11/2017 ukončení EU přehodnocení
- 2/2018 – zahájení referralu Art. 20 EC na podkladě 7případů potenciálně fatálních imunitních reakcí postihující CNS, játra a další orgány
- 3/2018 – okamžité pozastavení registrace a stažení z oběhu v EU, včetně použití v klinických hodnoceních – na základě 12 případů (3/12 fatální) encefalitidy/ meningoencefalitidy
- Benefit/risk negativní
- MAH v průběhu hodnocení požádal o zrušení registrace

Děkuji za pozornost

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