

**Agence fédérale des médicaments  
et des produits de santé**

**From Risk Management Plan to Risk Minimization  
Activities**

**New Royal Decree: Status and General Explanation  
Role of the Pharmacovigilance Department in RMP/RMA  
handling**

Thierry ROISIN – BRAS 28/5/2013



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**2 topics:**

- 1) New legal framework in pharmacovigilance**
- 2) Practical aspects concerning RMPs**



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## New legal framework as regards pharmacovigilance of medicinal products for human use

- Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards Pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (specific provisions on centrally authorised products and EMA tasks)
  - Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (nationally authorised products and common provisions)
- ⇒ Adopted by both Council and EU parliament and publication on 31 Dec 2010
- ⇒ Most of the provisions had to come into force in July 2012



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## New legal framework as regards pharmacovigilance of medicinal products for human use

Transposition of the Directive: current situation in Belgium

- **modification Law 25.3.1964: done (law 3.8.2012, published on 11.9.2012)**
- **amending RD 14.12.2006: ongoing**



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## GVPs (I)

European Medicines Agency - Pharmacovigilance - Good pharmacovigilance practices - Windows Internet Explorer

Final GVP chapters

Document(s)	Language	Status	First published	Last updated	Effective Date
Guideline on good pharmacovigilance practices: Module I - Pharmacovigilance systems and their quality systems	(English only)	adopted	25/05/2012		02/07/2012
Guideline on good pharmacovigilance practices: Module II - Pharmacovigilance system master file	(English only)	adopted	25/05/2012	12/04/2013	12/04/2013
Guideline on good pharmacovigilance practices: Module III - Pharmacovigilance procedures	(English only)	adopted	14/12/2012		12/12/2012
Guideline on good pharmacovigilance practices: Module IV - Pharmacovigilance audits	(English only)	adopted	13/12/2012		12/12/2012
Guideline on good pharmacovigilance practices: Module V - Risk management systems	(English only)	adopted	25/05/2012		02/07/2012
Guideline on good pharmacovigilance practices: Module VI - Management and reporting of adverse reactions to medicinal products	(English only)	adopted	25/05/2012		02/07/2012
Guideline on good pharmacovigilance practices: Module VII - Periodic safety update report	(English only)	adopted	25/05/2012		02/07/2012
Guideline on good pharmacovigilance practices: Module VIII - Post-authorization safety studies	(English only)	adopted	25/05/2012	25/04/2013	25/04/2013

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## GVPs (II)

European Medicines Agency - Pharmacovigilance - Good pharmacovigilance practices - Windows Internet Explorer

Guideline on good pharmacovigilance practices: Module VIII - Post-authorization safety studies

Document(s)	Language	Status	First published	Last updated	Effective Date
Guideline on good pharmacovigilance practices: Module VIII - Post-authorization safety studies	(English only)	adopted	25/05/2012	25/04/2013	25/04/2013
Guideline on good pharmacovigilance practices: Module IX - Signal management	(English only)	adopted	25/05/2012		02/07/2012
Guideline on good pharmacovigilance practices: Module X - Additional monitoring	(English only)	adopted	25/04/2013		25/04/2013
Guideline on good pharmacovigilance practices: Module XI - Safety communication	(English only)	adopted	24/02/2013		13/02/2013

**Related links**

Module XIII on incident management is no longer under development. All topics originally intended to be covered in this module are now to be included in module XII.

Where GVP modules refer to the European Medicines Agency's and the Heads of Medicines Agencies' procedural advice on referral procedures for safety reasons, consult:

► Questions and answers: Urgent Union procedure (Article 137f)

**Final GVP Annex I - Definitions**

Document(s)	Language	Status	First published	Last updated	Effective Date
Guideline on good pharmacovigilance practices: Annex I - Definitions	(English only)	adopted	16/04/2013	13/12/2012	13/12/2012

**Final GVP annex II - Templates**

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## Legislation : main changes (I)

«OLD» LEGISLATION	«NEW» LEGISLATION
DDPS	<u>Summary of DDPS + Pharmacovigilance system master file</u>
RMP if required	RMP for <u>all applications</u> (proportionate to risks)
Definition of ADR: under normal conditions	Definition of ADR: also in case of <u>off label use, misuse,...</u>
SERIOUS ADRs to EV	SERIOUS and <u>NON SERIOUS</u> ADRs to EV
Patient reporting: no legal basis	Patient reporting: <u>legal basis</u>



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## Legislation : main changes (II)

«OLD» LEGISLATION	«NEW» LEGISLATION
PSURs for all MAs	PSURs submission <u>in function of risks</u>
PSUR WS on voluntary basis	PSUR WS: <u>legal basis</u>
PSUR to be sent to all CA's	PSUR repository by EMA
Renewal submission 6 month before expiration of validity	Renewal submission <u>9</u> month before expiration of validity
Signal detection: no legal basis	Signal detection: <u>legal basis</u>
PASS: no legal basis	PASS: <u>legal basis</u>
PAES: no legal basis	PAES: <u>legal basis</u>



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## Legislation : main changes (III)

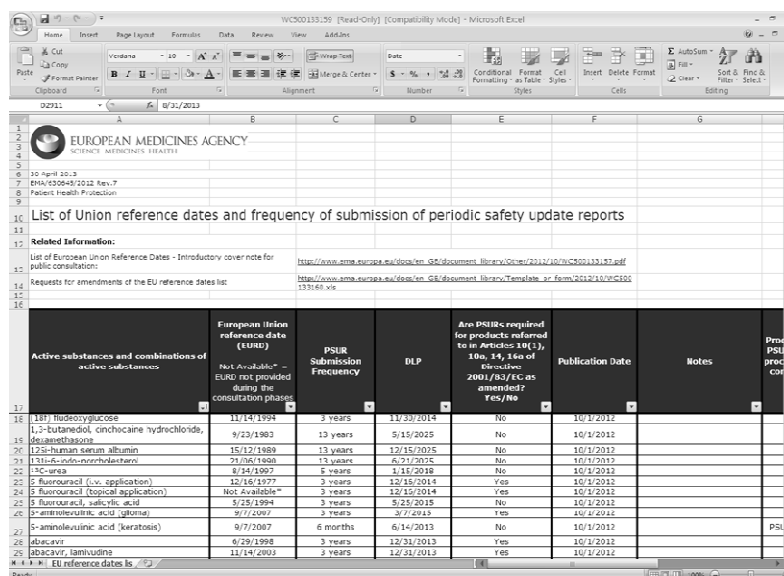
«OLD» LEGISLATION	«NEW» LEGISLATION
QPPV also at national level	QPPV at EU level only + <u>contact person</u> if QPPV not located in Belgium
Additional monitoring: no legal basis	Additional monitoring: <u>legal basis</u>
Monitoring of literature by all MAH	<u>Monitoring of literature by EMA</u>
PhVWP	<u>PRAC</u> <u>New urgent union procedure</u> <u>More transparency</u> ...

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## Legislation : main changes (IV)



Active substances and combinations of active substances	European Union reference date (EURD)	PSUR Submission Frequency	DLP	Are PSURs required for products referred to in Articles 10(1), 10a, 14, 14a of Directive 2001/83/EC as amended?	Publication Date	Notes	PSUR procedure
17 (18) Hydroxyglucose	11/14/1994	3 years	11/30/2014	No	10/1/2012		
18 1,3-butanediol, cinchocaine hydrochloride, bisulfite/sulfite	9/23/1993	13 years	5/15/2025	No	10/1/2012		
19 12-0-hydroxy serum albumin	15/12/1989	13 years	12/15/2025	No	10/1/2012		
20 131I-L-tyrosine-neuroblastoma	21/06/1998	13 years	6/21/2025	No	10/1/2012		
21 131I-L-tyrosine	9/24/1997	5 years	3/13/2018	No	10/1/2012		
22 5-Fluorouracil (i.v. application)	12/16/1977	3 years	12/15/2014	Yes	10/1/2012		
23 5-Fluorouracil (topical application)	Not Available*	3 years	12/15/2014	Yes	10/1/2012		
24 5-Fluorouracil, sulfuric acid	5/28/1994	3 years	5/28/2015	No	10/1/2012		
25 5-aminolevulinic acid (topical)	9/7/2007	3 years	3/7/2015	Yes	10/1/2012		
26 5-aminolevulinic acid (keratosis)	9/7/2007	6 months	6/14/2013	No	10/1/2012		
27 abiraterone	6/29/1998	3 years	12/31/2013	Yes	10/1/2012		
28 abiraterone, tamoxifen	11/14/1993	3 years	12/31/2013	Yes	10/1/2012		

## Legislation : main changes (V)



23 April 2013  
EMA/CHMP/128533  
Patient Health Protection

7 Watlington Drive • Canary Wharf • London E14 4HS • UK  
Telephone: +44 (0)20 7582 1000 • Facsimile: +44 (0)20 7582 1001  
E-mail: info@ema.europa.eu • Website: www.ema.europa.eu  
an agency of the European Union

List of medicinal products under additional monitoring

Related Information:

Additional monitoring explained: [http://www.ema.europa.eu/ema/ema\\_images/pdfs/legislation/legislation\\_monit\\_20120513.pdf](http://www.ema.europa.eu/ema/ema_images/pdfs/legislation/legislation_monit_20120513.pdf)  
Good Pharmacovigilance Practice Module: [http://www.ema.europa.eu/ema/ema\\_images/pdfs/legislation/legislation\\_monit\\_20120513.pdf](http://www.ema.europa.eu/ema/ema_images/pdfs/legislation/legislation_monit_20120513.pdf)

Product name	Active Substance (s)	Reason (s) on list	Marketing Authorisation Holder (s)
Adacur	lorazepam	New active substance	Alkermes UK Ltd
Adcetris	Brexitucimab vedotin	New active substance, conditional authorisation, PASS <sup>1</sup>	Takara Global Research and Development Center Ltd.
Aducanumab	Lamivudine	Authorised under exceptional circumstances, PASS	Genzyme Europe B.V.
AMTID	Fluorouracil [14F]	New active substance	ES Lilly Netherlands B.V.
AMTID	ofatumumab	Conditional authorisation, PASS	Glaxo Group Limited
Arjance	Salivabine	Authorised under exceptional circumstances	Glaxo Group Limited
ATryn	amprolium alpha	Authorised under exceptional circumstances, PASS	OTC Biopharmaceuticals UK Limited
Bactera	Bismuthum	New active substance	Alkermes UK Ltd
Becton	Rivastigmine	New active substance	Autolux Pharma Europe B.V.
Becton	Meningococcal group B vaccine (ovim, component, adsorbed)	New active substance	Novartis Vaccines and Diagnostics S.r.l.
Bio-Rar	Colistin	New active substance	Microlab Pharma Europe Ltd.
Bosulf	Bosutinib	New active substance, conditional authorisation, PASS	Pfizer Limited
Breatac Generix	acetic acid/bromide	New active substance, PASS	Almirall, S.A.
Cephalix	Vancomycin	New active substance, conditional authorisation	AdvaZentiva AB
Cephalix	Rivaroxaban, atroxibenzolide	Authorised under exceptional circumstances	Merck AB
Chempix	Vancomycin	PASS	Pfizer
Cinza	α1 inhibitor, human	PASS	VioPharma SRL
Cleopren emulsion for injection 0.5 mg/ml	Cleopren	New active substance	The Medicines Company UK Limited
Condella	unacode	New active substance	Almirall, S.A.
Copyma	Copper (II) chloride	New active substance	SpaRMe S.r.l.
Dacogen	Decitabine	New active substance	Janssen-Cilag International B.V.
Dendur	Benzocaine/benzocaine	New active substance	Olsen Corporation



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## Legislation : main changes (VI)



**Postponed activities** (Ref: 30 November 2012 EMA/719049/2012)

Patient Health Protection Implementation of the pharmacovigilance legislation Activities to be undertaken in 2013)

Activities which require additional funding are delayed:

Literature monitoring:

Start of the new outsourced business process and inclusion of case reports in the EudraVigilance database.

EudraVigilance:

Delivery of enhanced EudraVigilance functionalities.

Conduct of the EudraVigilance audit (postponed to at least Q4 2015 because of the delay in the development work).

PSURs:

Delivery of a PSUR repository.

Introduction of the single PSUR assessment process for NAPs, with input from analyses of ADR data.

Risk management system:

Define key indicators for measuring the effectiveness of risk minimisation and establish a monitoring system.

Transparency and communication:

Delivery of the EU medicines web portal.

Introduction of the public hearing concept for other referral procedures than the Urgent Union procedure (until experience has been obtained with this concept in the context of the Urgent Union procedure).



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## PRAC

### New scientific committee within the Agency Pharmacovigilance Risk Assessment Committee - Reg art. 56(1)(aa)

**Mandate** – Reg. art. 61a §6

**“ All the aspects of the risk management of medicines ... having due regard to the therapeutic effect of the medicinal product ...”:**

- Recommendations to CHMP and CMD(h) on Phvig issues
- Role in agreement and monitoring of RMPs
- Prioritisation and review of emerging safety signals
- Review of PSUR assessments
- Evaluation of protocols and results of PASS
- Decision on products under additional monitoring
- ...



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## PRAC - composition

Appointed by each  
Member State:



- 1 member + alternate
- 27 + EEA countries non voting members



Appointed by the European  
Commission following a public call  
for expressions of interest:



- 1 patient organisations rep + alternate
- 1 healthcare professionals rep + alternate
- 6 members to ensure relevant expertise available



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## PRAC – activities (I)

Activity	Involvement
Risk Management Systems	Agreement on RMPs + monitoring their effectiveness
Periodic Safety Update Reports PSURs	List of harmonised submission frequencies and substances, assessment + recommendation
Eudravigilance + Periodic Safety Update Reports repository	Functional specifications, any substantial changes
Medicines subject to additional monitoring	Addition to/removal from list, extension of timeframe, symbol
Signal Detection	Initial analysis + prioritisation assessment + recommendations



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## PRAC – activities (II)

Activity	Involvement
Urgent Safety Procedures for the EU	Assessment, public hearings, recommendations
Post Authorisation Safety Studies	Consultations on requests (pre and post MA), assessment of protocols (incl. amendments) + recommendations, assessment of results + recommendations
Literature Adverse Drug Reactions monitoring	Consultation on list of active substances and medical literature subject to monitoring?
Safety announcements	Advice



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## PRAC

### •Interaction with CHMP and CMD(h)

▪PRAC provides recommendations to CHMP and CMD(h) – Reg. art. 56(1)(aa)



▪CHMP / CMD(h) shall rely on the scientific assessment and recommendations of PRAC for the fulfilment of its phvlg tasks, including the approval of risk management systems and monitoring their effectiveness – Reg. art. 5(2) / Dir. art. 27

▪Explanation on the scientific grounds for differences if opinion / agreement is not in accordance with PRAC recommendation



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## PRAC

### Decision-making process

PSUR  
PASS

Union procedures (art. 30\*, 31\*, 107i)

CMD(h) (no CAP)

Position = maint., var.,  
susp., revoc.

If consensus:  
agreement

MS: adopt measures

MAH: submit variation

PRAC recommendation:  
regulatory action

CHMP (at least 1 CAP)

Opinion = maint., var.,  
susp., revoc.

COMMISSION

NO consensus:  
position majority

Decision  
addressed to MS

Decision  
modifying MA  
(CAP)

\*if triggered by safety concern

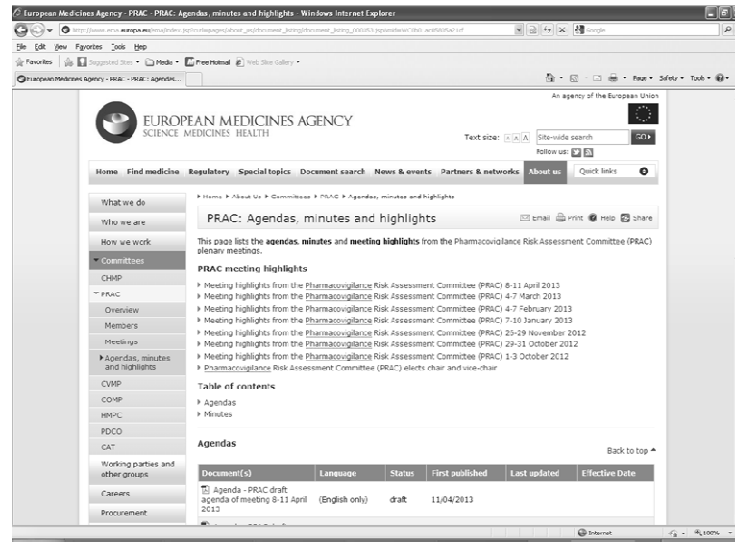


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## Strengthened transparency and communication



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## RMP: practical aspects (I)

RMP as part of the MA application:

- module 1.8.2.
- Pharmacovigilance assessors in charge of the assessment of the RMP
- Pharmacovigilance file manager in charge of the management of the RMP
- Coordination of the file management by DG PRE

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## RMP: practical aspects (II)

RMP submitted after the MA has been granted:

2 situations:      -first RMP  
                         -update of RMP (when: see GVP module V)

In both cases, RMP may be introduced:      -as a variation  
   -with a PSUR  
   -with a renewal

-as a variation: RMP has to be introduced to DG POST - POST-AMM division ([dispatching@fagg-afmps.be](mailto:dispatching@fagg-afmps.be))

-with a PSUR: RMP has to be introduced to DG POST vigilance Division (e-mail: [psurh@afmps-fagg.be](mailto:psurh@afmps-fagg.be))

-with a renewal: RMP has to be introduced to DG POST - POST-AMM division ([dispatching@fagg-afmps.be](mailto:dispatching@fagg-afmps.be))

Please specify it in the cover letter !

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## RMP: practical aspects (III)

**Link between assessment of RMP – RMA**

**Assessors of RMA dossiers (BUM) work in collaboration with external experts and Pharmacovigilance (Vigilance) assessors if needed**

**Pharmacovigilance assessors involved in the establishment of the conditions on the MA → inform BUM in case of additional RMA**

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## RMP: practical aspects (IV)

**PASS requested by Belgian authority and only performed in Belgium**

- study protocol →
- interim reports → submission to R&D division DG PRE by CD ROM
- final report →



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## RMP: practical aspects (V)

**PASS requested by a CA with PRAC involvement**

	Protocols (including amendments), final reports of study		Interim reports if requested
	Direct submission by the MAII in Belgium	Submission by the MAII in Belgium via PRAC	Direct submission by the MAII in Belgium
Study performed in Belgium	X		X
Belgium rapporteur or RMS for the medicinal product		X	X
Medicinal product authorised in Belgium but Belgium not rapporteur nor RMS		X	



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## RMP: practical aspects (VI)

PASS initiated, managed and sponsored by a MAH

	Protocols (including amendments), interim reports if requested and final reports of study
	Transmission by the MAH via notification from the EU PASS Register
Study performed in Belgium	X
Belgium rapporteur or RMS for the medicinal product	X
Medicinal product authorized in Belgium but Belgium not rapporteur nor RMS	X



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## RMP: practical aspects (VII)

A circular letter will be published by FAHMP after publication of the modification of the RD 14.12.2006.



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Contact

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notre préoccupation**

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