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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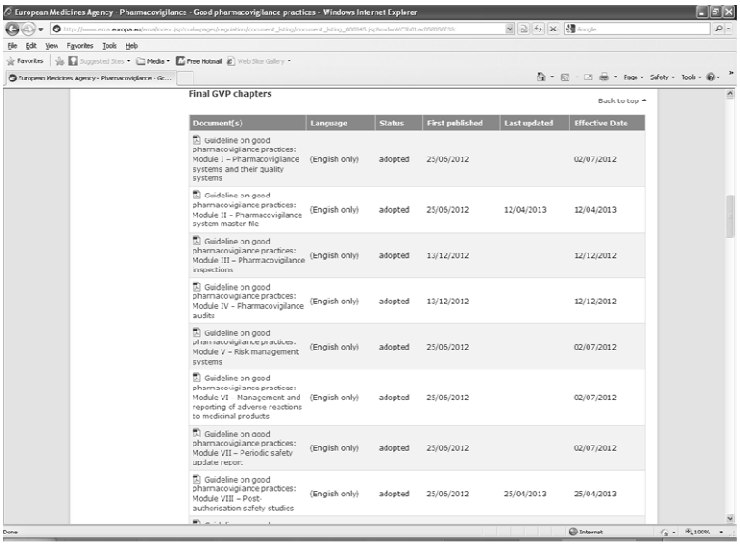
GVPs (I)



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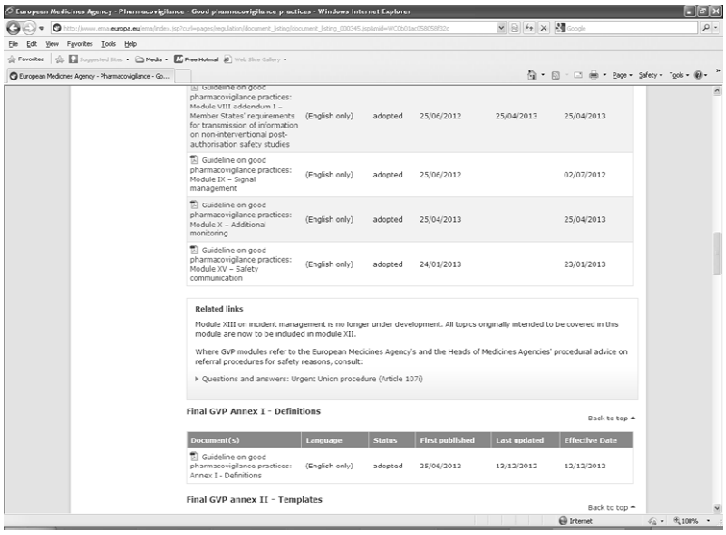
GVPs (II)



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Legislation : main changes (I)

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

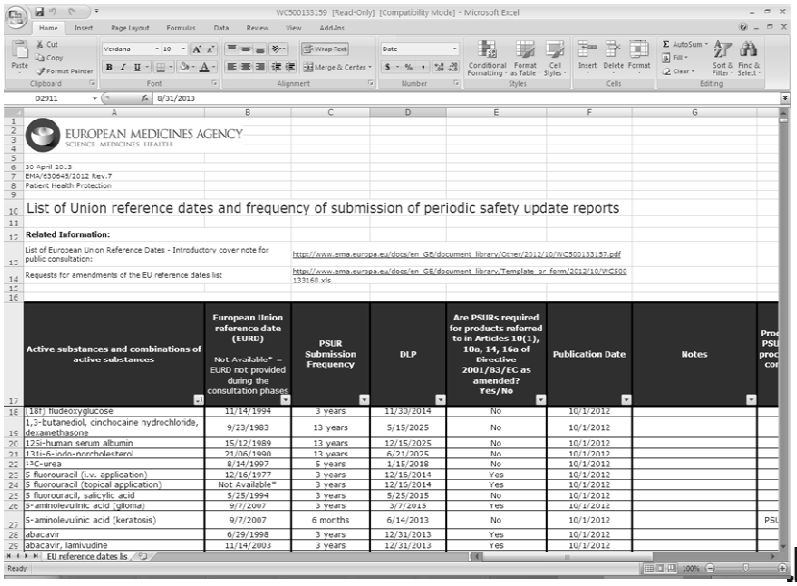
Legislation : main changes (II)

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

Legislation : main changes (III)

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

Legislation : main changes (IV)



Legislation : main changes (V)

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an agency of the European U

23 April 2013
EMA/145297/2013
Patient Health Protection

List of medicinal products under additional monitoring

Related Information:
Additional monitoring explained: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp
Good Pharmacovigilance Practice Modules: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

Product name	Active Substance (s)	Reason (s) on list	Marketing Authorisation Holder (s)
Adasuve	Loxapine	New active substance	Alexza UK Ltd
Adcetris	Brentuximab vedotin	New active substance, conditional authorisation, PASS[1]	Takeda Global Research and Development Centre Ltd.
Aldurazyme	Laronidase	Authorised under exceptional circumstances, PASS	Genzyme Europe B.V.
AMYVID	Florbetapir [18F]	New active substance	Eli Lilly Nederland B.V.
Arzerra	Ofatumumab	Conditional authorisation, PASS	Glaxo Group Limited
Arranon	Nelarabine	Authorised under exceptional circumstances	Glaxo Group Limited
ATryn	Antithrombin alpha	Authorised under exceptional circumstances, PASS	GTC Biotherapeutics UK Limited
Benlysta	Belimumab	New active substance	Glaxo Group Ltd
Besivance	Besifloxacin	New active substance	Bausch & Lomb Europe B.V.
Bexsero	Meningococcal group B vaccine (rDNA, component, adsorbed)	New active substance	Novartis Vaccines and Diagnostics S.r.l.
BindRen	Colestilan	New active substance	Mitsubishi Pharma Europe Ltd.
Bosulif	Bosutinib	New active substance, conditional authorisation, PASS	Pfizer Limited
Bretaris Genuair	Aclidinium bromide	New active substance, PASS	Almirall, S.A.
Caprelsa	Vandetanib	New active substance, conditional authorisation	AstraZeneca AB
Cepilene	Histamine dihydrochloride	Authorised under exceptional circumstances	Meda AB
Champix	Varenicline	PASS	Pfizer
Cinryze	c1 inhibitor, human	PASS	ViroPharma SPRL
Clevprex emulsion for injection 0.5 mg/ml	Clevidipine	New active substance	The Medicines Company UK Limited
Constella	Linaclotide	New active substance	Almirall, S.A.
Cuprymina	Copper (64Cu) chloride	New active substance	Sparkle S.r.l
Dacogen	Decitabine	New active substance	Janssen-Cilag International N.V.
Desolor	Desogestrel/Eth	New active substance	Orion Corporation

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Legislation : main changes (VI)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

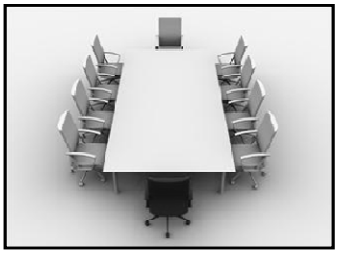
" All the aspects of the risk management of medicines … having due regard to the therapeutic effect of the medicinal product …":

- 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
- …

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

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

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

PRAC

•**Interaction with CHMP and CMD(**h)

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

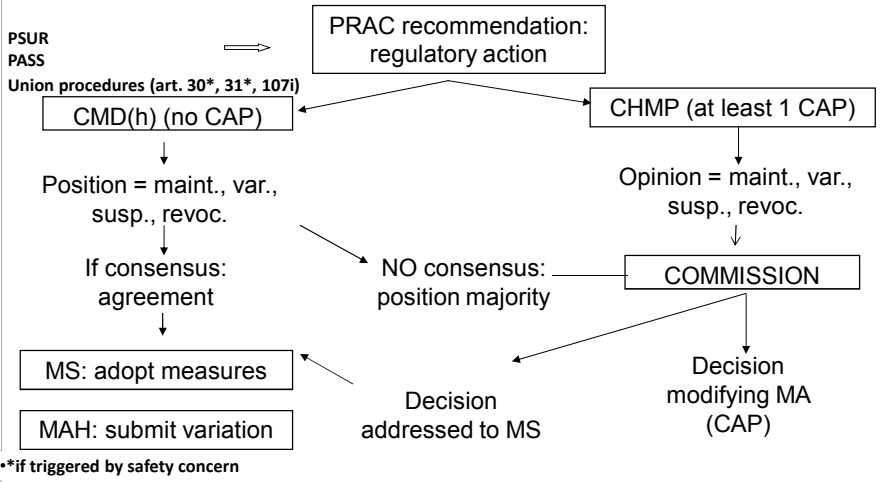
⇩

▪**CHMP / CMD(h) shall rely on the scientific assessment and recommendations of PRAC for the fulfilment of its phvig 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**

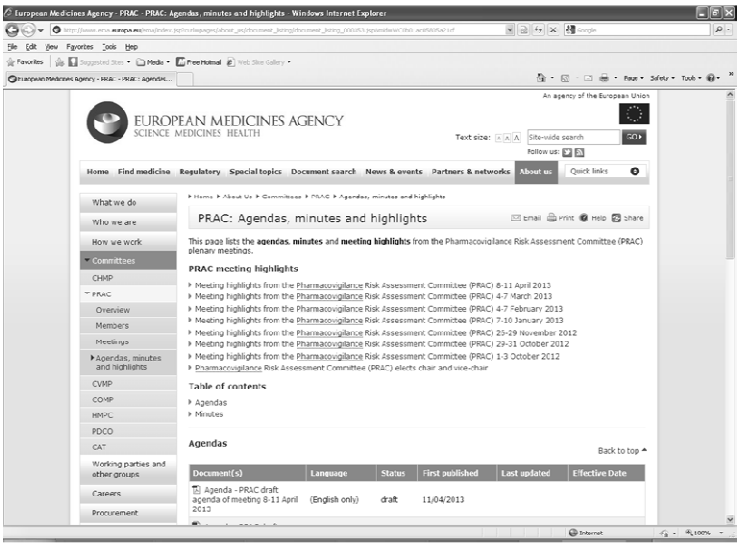
PRAC

Decision-making process



•***if triggered by safety concern**

Strengthened transparency and communication



RMP: practical aspects (I)

RMP as part of the MA application:

-module I.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

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)**

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

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

Please specify it in the cover letter !

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

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 →

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 MAH in Belgium	Submission by the MAH in Belgium via PRAC	Direct submission by the MAH 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	

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

RMP: practical aspects (VII)

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

Contact

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