Difference between EU-RMP and JP-RMP

- Those features perspective

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Risk Management

All medicines have some risks. When a medicine is given an authorisation, this means that there is enough evidence to prove that for the average patient the benefits of the medicine should be greater than the risks. However, the more the risks are reduced the better it is for the patient and the better the benefit-risk balance. This is the main purpose of "risk management" and how to do this is described in a risk management plan.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500129593.pdf

Risk-management plans

- Pharmacovigilance activities to identify and monitor those risks
- Risk-minimisation activities to endeavour to prevent them
  - Routine activities are mandatory for every product.
  - Additional activities are designed for specific safety concerns with the most important health impact.

Good pharmacoVigilance Practice

- Self-standing guidance on pharmacovigilance replacing Volume 9A
- Addressed to EU Marketing Authorisation Holders, Competent Authorities in Member States and Agency
- Developed within EU network
- 8 weeks public consultation
- 2 types of 'Chapters':
  - Modules for major processes
  - Product or populations specific (P)
- GVP structure:
  - A: Introduction
  - B: Structures and processes
  - C: Operation of the EU network

Good pharmacoVigilance Practice (GVP)

Module I Pharmacovigilance systems and their quality systems	**Module II** Pharmacovigilance system master file	**Module III** Pharmacovigilance inspections
Module IV Pharmacovigilance audits	**Module V** Risk management systems	**Module VI** Management and reporting of ADRs Publication of Revision 1 as final Q4 2013
Module VII Periodic safety update reports Publication of Revision 1 as final Q4 2013	**Module VIII** Post-authorisation safety studies	**Module IX** Signal management
Module X Additional monitoring	**Module XI** Public participation *Public consultation Q2 2014*	**Module XII** Continuous pharmacovigilance *Public consultation Q1 2014*
Module XIV International cooperation *Public consultation Q1 2014*	**Module XV** Safety communication	**Module XVI** Risk minimisation measures *Publication as final Q4 2013*
P I – Vaccines *Publication as final Q4 2013*		

Under development | Published | Public consultation

Dr. Arlett, 7th Stakeholder Forum on the Implementation of th new **Pharmacovigilance** Legislation

Contents of EU-RMP

Part I	**Product Overview**
Part II	**Safety Specification** Module SI Epidemiology of indication and target population Module SII Non-clinical part of Safety Specification Module SIII Clinical trial exposure Module SIV Populations not studied in clinical trials Module SV Post-authorisation experience Module SVI Additional EU requirements for Safety Specification Module SVII Identified and potential risks (non-ATMPs) Module SVIIa Identified and potential risks (ATMPs) Module SVIII Summary of safety concerns
Part III	**Pharmacovigilance Plan**
Part IV	**Plans for post-authorisation efficacy studies**
Part V	**Risk Minimisation Measures**
Part VI	**Summary of the risk management plan**
Part VII	**Annexes**

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25 July 2013
EMA/465932/2013 Rev.1[1]
Patient Health Protection

Guidance on format of the risk management plan (RMP) in the EU – in integrated format

Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Name of Marketing Authorisation Holder or Applicant:	
Number of medicinal products to which this RMP refers:	Choose one of the following: • 1 • 2 • 3 • 4 • 5 • 6
Product(s) concerned (brand name(s)):	

Data lock point for this RMP	<Enter a date>	Version number	<Enter a version no>
Date of final sign off	<Enter a date>		

[1] Please note that under section VI.1.4 Summary table of Risk Minimisation Measures "Copy table from Part V: 5.2" should have read "Copy table from Part V: V.3"

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SCIENCE MEDICINES HEALTH

25 July 2013
EMA/465933/2013 Rev.1[1]
Patient Health Protection

Guidance on format of the risk management plan (RMP) in the EU for Generics

Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Name of Marketing Authorisation Holder or Applicant:	
Number of medicinal products to which this RMP refers:	Choose one of the following: • 1 • 2 • 3 • 4 • 5 • 6
Product(s) concerned (brand name(s)):	

Data lock point for this RMP	<Enter a date>	Version number	<Enter a version no>
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SIV.1 Limitations of adr detection common to clinical trial development programmes

Clinical trial development programmes are unlikely to detect the following types of adverse reactions due to well-known inherent limitations. Based on the number of patients exposed, the duration of patient exposure, total dose of medicine, action of medicine etc., discuss what could have been detected.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	<E.g. 12,600 patients were exposed over the whole CT programme>	<E.g. ADRS with a frequency greater than 1 in 4,200 could be detected if there were no background incidence>
Due to prolonged exposure	<E.g. 3000 women were exposed to X for more than 4 years during which time there were no cases of endometrial carcinoma. 42 women in the treated experienced endometrial hyperplasia compared with 35 in the non-exposed group (2000)>	<E.g. There does not appear to be an effect on endometrial proliferation during the first 4 years of treatment. X is thought to .....etc.>
Due to cumulative effects	<e.g. specific organ toxicity>	
Which have a long latency		

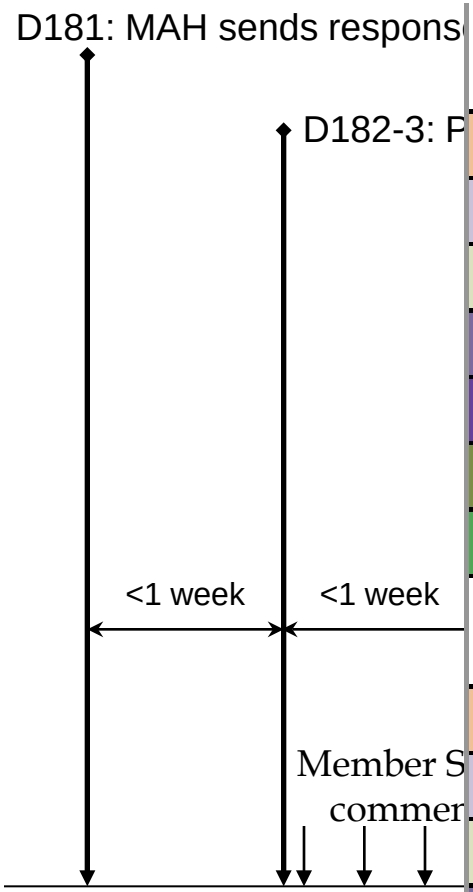
Steps to be fixed in EU

- Both CHMP and PRAC Rapporteurs start assessing the dossier at Day 0
- CHMP Rapporteur's draft AR circulated first
- PRAC Rapporteur considers CHMP draft AR and circulates the draft RMP AR
- Peer review and MS comments (PRAC + CHMP)
- PRAC RMP AR updated (AR template designed for the process; one single document concept)

Steps to be publish in EU

- Applicant to provide 1st draft of RMP – summary at the time of submitting application
- Preparation of RMP summary: EMA, Rapporteurs and assessors
- Wherever necessary, review by patients and healthcare professionals during preparation
- Industry to receive document prior to its publication

Steps to be fixed in EU



D121-180 - second stage	
Restart	121
PRAC AR	150
CHMP AR	**150**
updated PRAC AR	159
PRAC	162-166
updated CHMP AR	173
CHMP	177-180
D181-210 - third stage	
Restart	181
PRAC AR	**182-183**
CHMP AR	**189**
updated PRAC AR	190
PRAC	192-196
updated CHMP AR	203
CHMP	217-210

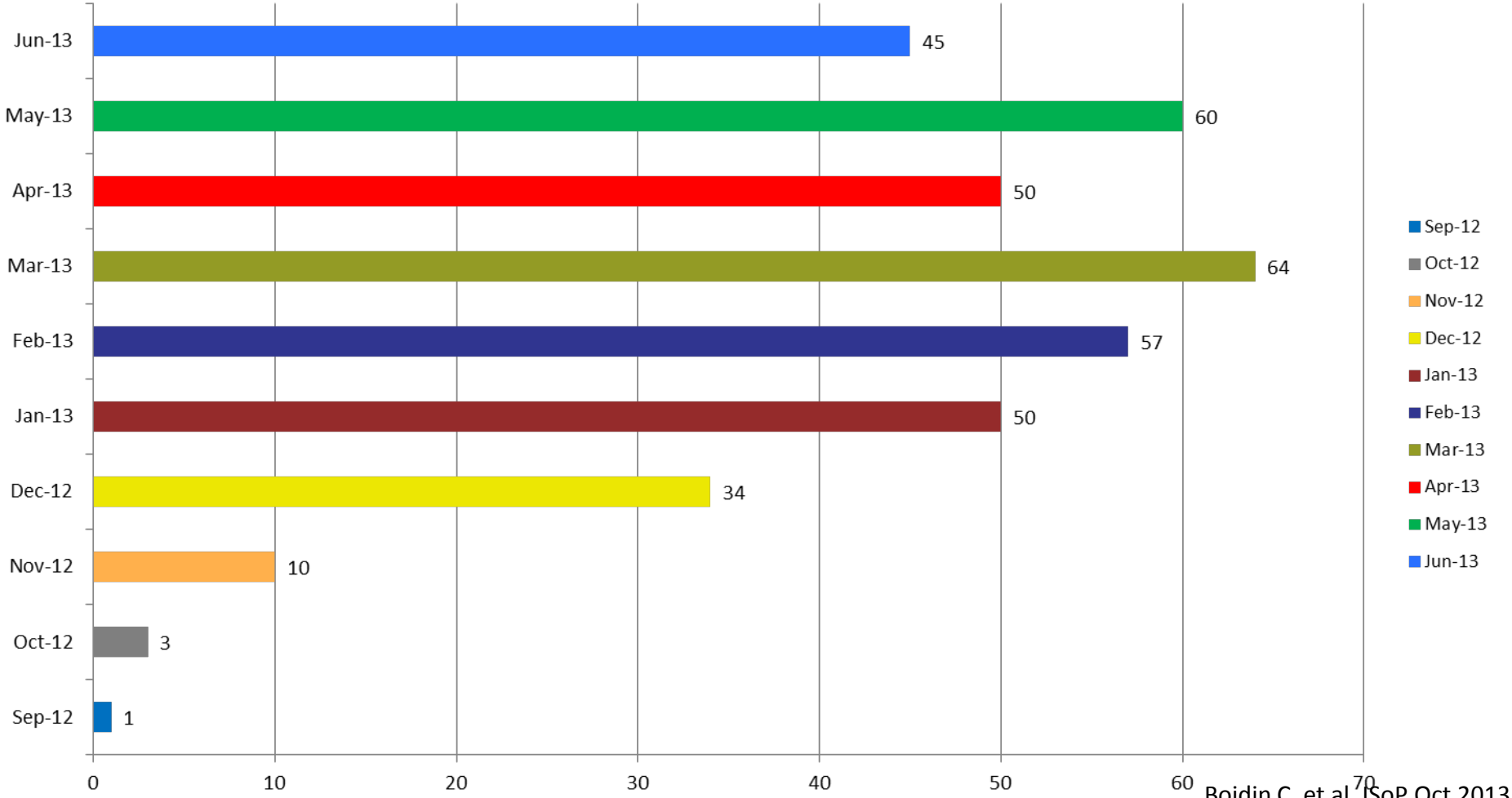
Real world of EU-RMP

- EU-RMPs for initial MAs for CAP with a positive CHMP opinion between 2010 and 2012 were selected.
- 1,972 safety issues were identified from 121 EU-RMPs
  - The number of safety issues for a product was 4 – 36.
- The distribution of activities was
  - 98 products with additional PhV activities (81% of the total)
  - 38 with additional Rmin activities (31% of the total)
    - 31 products had both additional PhV and additional Rmin activities.
- 16 products (13% of the total) did not have any additional activities.

Boidin C. et al, ISoP Oct 2013

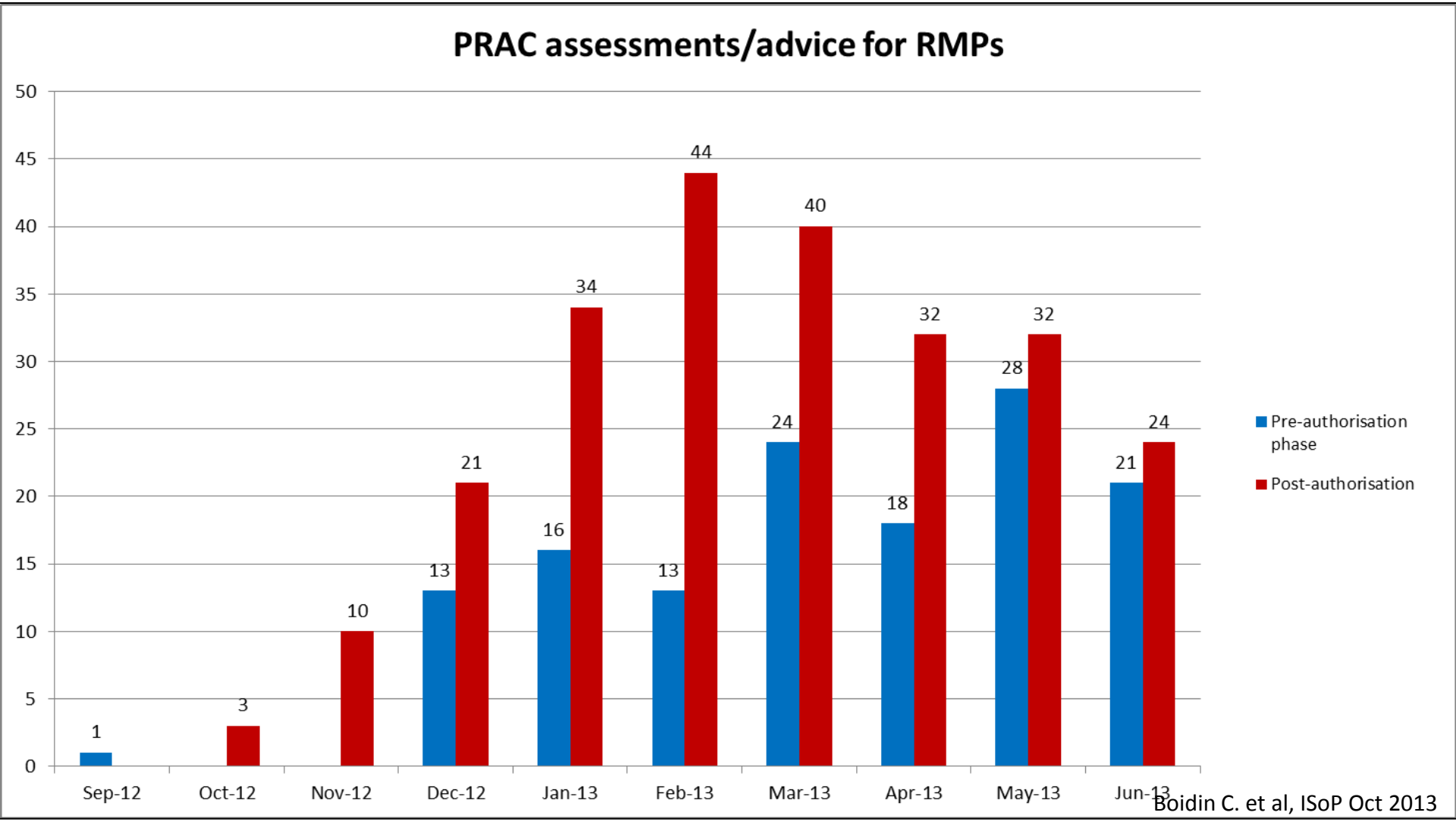
Real world of EU-RMP

Total Number of PRAC assessments/advice for RMPs - 374



Boidin C. et al, ISoP Oct 2013

Real world of EU-RMP



Boidin C. et al, ISoP Oct 2013

Real world of EU-RMP

- Additional PhV activities were designed for
  - identified risks 26%
  - potential risks 36%
  - missing information 38%
- Additional Risk minimisation activities
  - identified risks 49%
  - potential risks 30%
  - missing information 21%
- Pharmacovigilance activities
  - clinical trials 47%
  - observational studies 36%
  - active surveillance 16%
- Risk minimisation the activities
  - for healthcare-professional education 71%
  - for patient education 29%

Boidin C. et al, ISoP Oct 2013

Similarity

- Correspond to ICH-E2E
- To bridge gaps with real world
  - Limitation of clinical trial data
    - Population, duration, concomitant products etc.

Timing of the submission

- Initial MAA
- Extension of indication
- Line extension
- New manufacturing process of a biotechnologically-derived product
- At the request of the EMA or NCA

- Initial MAA
- New indication
- New dosage
- At the timing of risk newly identified

Updates of the RMP

- If information becomes available that has an impact on the benefit-risk profile of the medicinal products included in the RMP
  - e.g. when new information is received that may impact on the current safety specification, pharmacovigilance plan, assumptions regarding efficacy or risk-minimisation measures, or within 60 days of an important (pharmacovigilance or risk-minimisation) milestone being reached
- At the request of a competent authority.

- Depend on post-authorisation circumstance
  - e.g. when new information is received that may impact on the current safety specification, pharmacovigilance plan, assumptions regarding efficacy or risk-minimisation measures, or within 60 days of an important (pharmacovigilance or risk-minimisation) milestone being reached

Publication of RMP summary

- Initiates ?
- Contents of Summary
  - Overview of disease epidemiology
  - Summary of the benefit/efficacy
  - Summary of main safety concerns (identified, potential and missing information)
  - Summary of risk minimisation measures by safety concern (routine and additional)
  - Planned post-authorisation (safety and efficacy) development plan
  - Major changes over time

- Initiated in Aug. ’13
- Summary of risk management plan
  - safety concerns
  - efficacy to be studied after authorisation
- Summary of PhV plan
- Summary of post-authorisation efficacy study
- Summary of risk minimisation plans

Reporting

- PSUR
  - PBRER

- Periodic Safety Report
  - Japanese data
  - PBRER

Difference?

- Broader in EU?
  - Coverage of ‘Missing information’ ?
  - Data from off label use
- Modifications are required to be adopted each region/country in EU.
  - Diversities in EU

Additional EU requirements

Covers potential safety concerns not included in ICH E2E:

- Harm from overdose
- Transmission of infectious agents
- Misuse for illegal purposes
- Medication errors
  - Any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer (wrong medication, dose, route of administration or patient)
  - Assess potential for ME during development and design phase of the product with regard to naming, presentation, instructions for use and labelling
- (Paediatric) off-label use
- Paediatric safety and efficacy issues identified in PIP

Expectation to RMP

- More meaningful data collection
  - More positive benefit/risk balance
    - Clarification of risk factors
    - Positioning in the real world
- Global data collection
  - Continuously from development to post-authorisation
  - Optimal dosage for all patients