EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The EU Risk Management Plan - a tool to address the uncertainties at the time of approval, and manage the risks of medicines

Health care uncertainty assessment workshop

Session 3: The challenges of health technologies – benefit/risk evaluation of medicinal products

Presented by Emil Cochino on 8 October 2015
Scientific Officer, Scientific and Regulatory Management Department

Disclaimer

The views and opinions expressed in this presentation are those of the speaker and may not represent the official view of the European Medicines Agency (EMA)

Summary of slides

EMA – who we are and what we do

Approval of medicines in EU – centralised procedure

Uncertainties at the time of approval

The need for the Risk Management Plan / legislative background

The RMP document

European Medicines Agency (EMA)

- ✓ a decentralised agency of the European Union (EU)
- ✓ Canary Wharf, London, UK
- ✓ Responsible for the evaluation and supervision of medicines for human and veterinary use

EMA

- ✓ scientific evaluation of applications for European Union (EU) **marketing authorisations** for human and veterinary medicines in the centralised procedure
- ✓ coordinates the EU's **safety-monitoring or 'pharmacovigilance' system** for medicines
- ✓ **Referrals** (safety), **Inspections** (GMP, GCP, GLP, PhV), **Telematics**
- ✓ **Stimulating innovation**: scientific advice, guidelines, assistance to SMEs, orphan designation, Innovation Task Force
- ✓ Hub for the **European network**: national regulatory authorities, EU Commission, EU Parliament, other EU agencies; also works closely with WHO and regulatory authorities of non-European nations

EMA supports research

Works across a wide number of topics and with a broad range of stakeholders, from research institutes, universities and public-private initiatives to the European Commission and EU Member States:

- ❑ As coordinator of a research project;
- ❑ as a participant in research activities;
- ❑ with an advisory role.

Examples:

- EMA is the coordinator for PROTECT (The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium - http://www.imi-protect.eu);
- EMA is a partner for ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe - www.advance-vaccines.eu).

Central authorisation of medicines

Medicines can be authorised by the centralised authorisation procedure or national authorisation procedures

EMA is responsible for the **centralised authorisation procedure** for human and veterinary medicines

Evaluation by the Agency's **Scientific committees** -> an opinion on whether the medicine should be marketed or not

Opinion is transmitted to the **European Commission**, which has the ultimate authority for granting marketing authorisations in the EU

Single marketing authorisation valid in all EU countries, as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway

Evaluation of initial Marketing Authorisation Applications

Eligible medicinal products -> Application for MA

Dossier is evaluated by Committees Rapporteurs' teams (up to 210 active days plus 'clock stops')

- ✓ CHMP responsible for overall assessment and Opinion
- ✓ PRAC assesses the prospective planning described in the RMP
- ✓ CAT for ATMPs

Assessment Reports comments from all EU MS

Opinion adopted by CHMP

European public assessment reports

Chapter 3: Benefit-Risk Balance:

- Benefit; Uncertainty in the knowledge about the beneficial effects
- Risks: Unfavourable effects; Uncertainty in the knowledge about the unfavourable effects
- Balance: Importance of favourable and unfavourable effects
- Benefit-risk balance: Discussion on the benefit-risk assessment

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

Example: Lenvima, assessment report is published on EMA website

Effect	Short Description	Unit	Placebo	Lenvatinib	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death	Months	3.6 (2.2, 3.7)	18.3 (15.1, NE)	Consistent and significant effect on PFS with a HR of 0.21 (0.14, 0.31)	See 'clinical efficacy' section
OS	Median time from randomization to death of any cause	Months	NE (14.3, NE)	NE (22.0, NE)	The OS data are confounded by crossover with a HR of 0.80 (0.57, 1.12)	
Unfavourable Effects						
Hypertension	Incidence of grade 3 or 4 events	%	3.8	42.9	The association with these risks is further supported by the analysis in the extended safety population The chosen dose of 24 mg is associated with important levels of dose reductions and interruptions	Numbers presented were taken from the DTC Randomized Safety Set (see 'clinical safety' section)
Proteinuria	Incidence of grade 3 or 4 events	%	0	10.7		
Liver events	Incidence of grade3 or 4 events	%	1	10.7		
Hypocalcaemia	Incidence of grade 3 and 4 events	%	0	4.9		
Diarrhoea	Incidence of grade 3 and 4 events	%	0	9.2		
Fatal AE	Incidence of treatment-related fatal AE	%	0	2.3	Uncertainties linked to low numbers	

Abbreviations: AE: adverse event; HR: hazard ratio; NE: not estimable; OS: overall survival; PFS: progression-free survival data cut-off dates : efficacy - PFS: 15 November 2013, OS:15 June 2014 ;safety: 25 March 2014.

Authorising medicines: What we know…

At the time of authorisation:

- ✓ Dossier of evidence submitted by the companies on quality, safety and efficacy
- ✓ Full assessment by the regulators
- ✓ Benefits must outweigh risks based on evidence from clinical trial program

What we know:

- ✓ Usually good evidence from clinical trials demonstrating efficacy in the specific indication and populations studied
- ✓ Good evidence from clinical trials on the most common adverse reactions

…and what we don't know

- Effectiveness of the product in normal clinical practice: compliance, resistance, populations not included in trials
- Full safety profile including *adverse drug reaction*s which are:
  - Rare
  - Delayed
  - From chronic exposure
  - From interactions
  - Medication errors
  - Off-label use
  - Associated with abuse/misuse
  - Associated with populations not yet studied in trials (e.g. children, very elderly, pregnancy, lactation, co-morbidity)

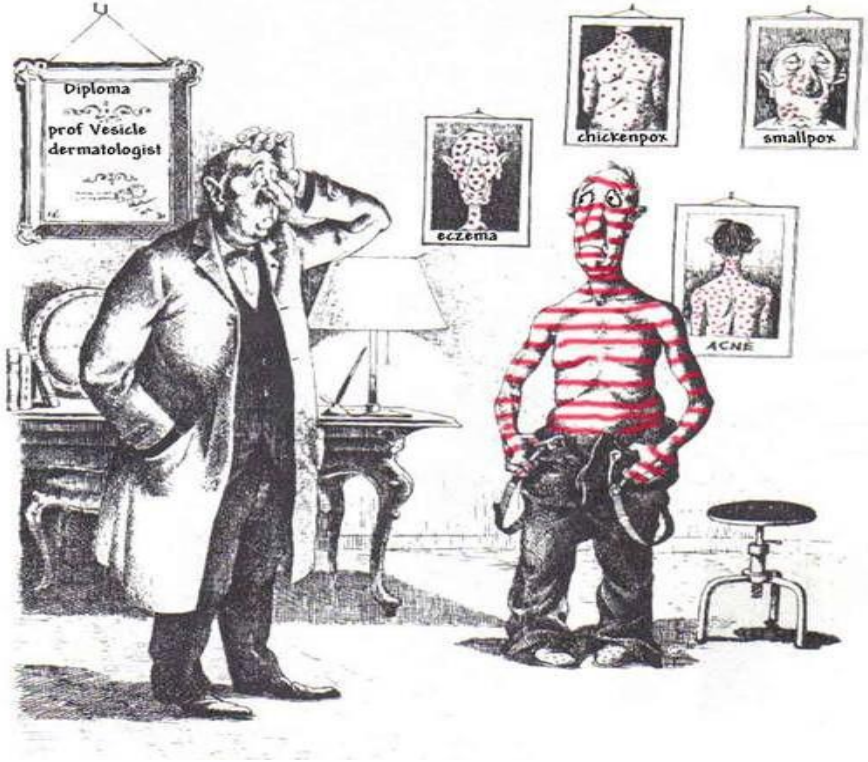
Table 1 — Chance that a very rare side-effect (0.01%) will not be observed

Number of patients treated	Chance of missing (%)
500	95.1
1000	90.5
2500	77.9
5000	60.7
7500	47.2
10000	36.8
15000	22.3
20000	13.5
25000	8.2
30000	5.0

Amery K Pharmacoepidemiology and Drug Safety, 8: 61±64 (1999)

Why the Concept of Risk Management?

- Some high profile safety issues warrant urgent regulatory actions (suspension, withdrawal)
- Pro-active monitoring of drug safety to evaluate changes in benefits and risks
- Changing environment of drug safety:
  - More information with better access
  - Increased expectations from health authorities, public and media



EU Legislation (as of 2 July 2012)

- ✓ **Directive 2010/84/EU** *amending*, as regards pharmacovigilance, **Directive 2001/83/EC** on the Community code relating to medicinal products for human use.
- ✓ **Regulation (EU) No 1235/2010** *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.
- ✓ **Commission Implementing Regulation (EU) 520/2012** on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC.

Legal Basis for Risk Management Plans

The application for MA shall be accompanied by [DIR Article 8(3) (iaa)]:

[…]

(ia) A summary of the applicant's **pharmacovigilance system** which shall include the following elements […]:

(iaa) The **risk management plan** describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a **summary** thereof.
The risk management system […] shall be **proportionate** to the risks and the need for post-authorisation data.

Risk Management Definition

Definition from 'CHMP Guidance on Risk Management Systems', now in DIR:

> **Risk management system**: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.
>
> **Risk management plan**: a detailed description of the risk management system.

Obligation is fulfilled by submitting a Risk Management Plan (RMP), in the format of the **EU-RMP** template, and maintaining it;

EU-RMP is legally binding;

RMP Requirements for MAH (I)

As part of the pharmacovigilance system, the marketing authorisation holder shall operate a risk management system for each medicinal product [DIR Article 104]

Holders of MA granted before 2 July 2012 shall not be required to operate a risk management system for each medicinal product [REG Article 21]

Legal basis for older MA: 'The Agency may impose the obligation to operate risk management system...' [REG Article 21 (2)]

RMP Requirements for MAH (II)

The marketing authorisation holder shall incorporate any **conditions or requirements** referred to in Articles 9(4) points (c)(ca)(cb)(cc), 10a, 14(7) and 14(8) in his **risk management system** [REG Article 14a]:

- Conditions and restrictions for safe and effective use
- Recommended measures for safe use
- Post-Authorisation Safety Studies (PASS)
- Post-Authorisation Efficacy Studies (PAES)
- Post-approval obligation for PASS / PAES
- Specific Obligations
- Exceptional Circumstances

RMP Requirements for MAH (III)

As part of the pharmacovigilance system, the marketing authorisation holder shall [DIR Article 104]:

3(d) <u>monitor the outcome of risk minimisation measures</u> which are contained in the risk management plan or which are laid down as conditions of MA.

3(e) <u>update the risk management system</u> and monitor pharmacovigilance data to determine

- if there are new risks
- if risks have changed
- if benefit-risk balance has changed

Guidance and Templates

Good Pharmacovigilance Practices (GVP) on Risk Management Systems (**Module V**)

- GVP is a key deliverable of the 2010 pharmacovigilance legislation
- Set of measures drawn up to facilitate the performance of pharmacovigilance in the EU
- Applicable to MAHs, the Agency and EU Competent Authorities and to medicines authorised centrally as well as at national level

EU Risk Management Plan Template (EU-RMP)

- A template was published on EMA website based on Annex I of Implementation Regulation 520/2012 and GVP Module V and consultation with pharmaceutical industry associations

Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
Scientific guidelines
Innovation Task Force
SME office
Paediatric medicine
Geriatric medicine
Orphan designation

Good pharmacovigilance practices

Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP apply to marketing-authorisation holders, the European Medicines Agency and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

Guideline on GVP

The **guideline on GVP** is divided into chapters that fall into two categories:

- modules covering major pharmacovigilance processes;
- product- or population-specific considerations.

Each chapter is developed by a team consisting of experts from the European Medicines Agency and from EU Member States.

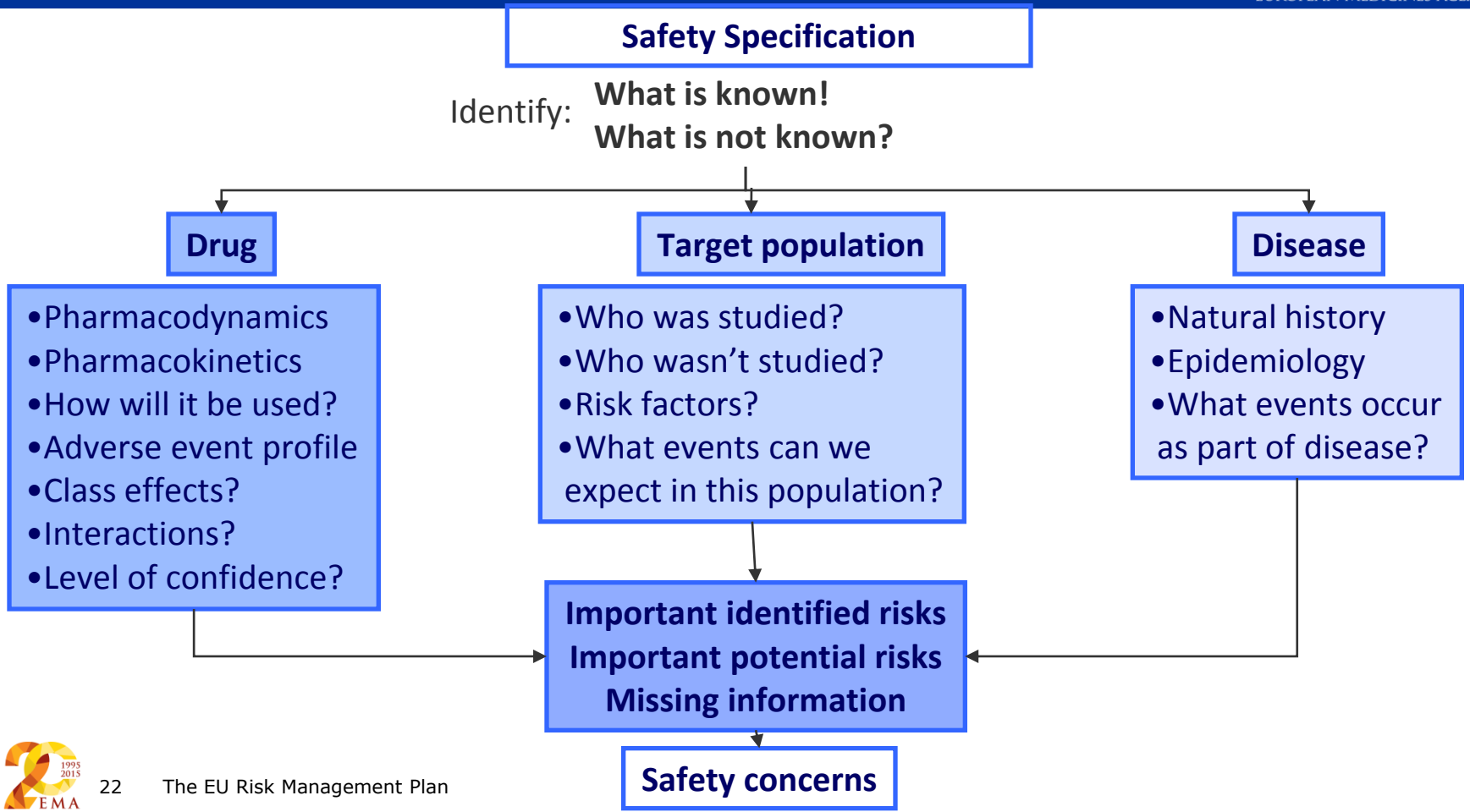
The guideline on GVP is a key deliverable of the 2010 pharmacovigilance legislation.

Modules covering major pharmacovigilance processes

GVP modules I to XVI cover major pharmacovigilance processes.

The RMP

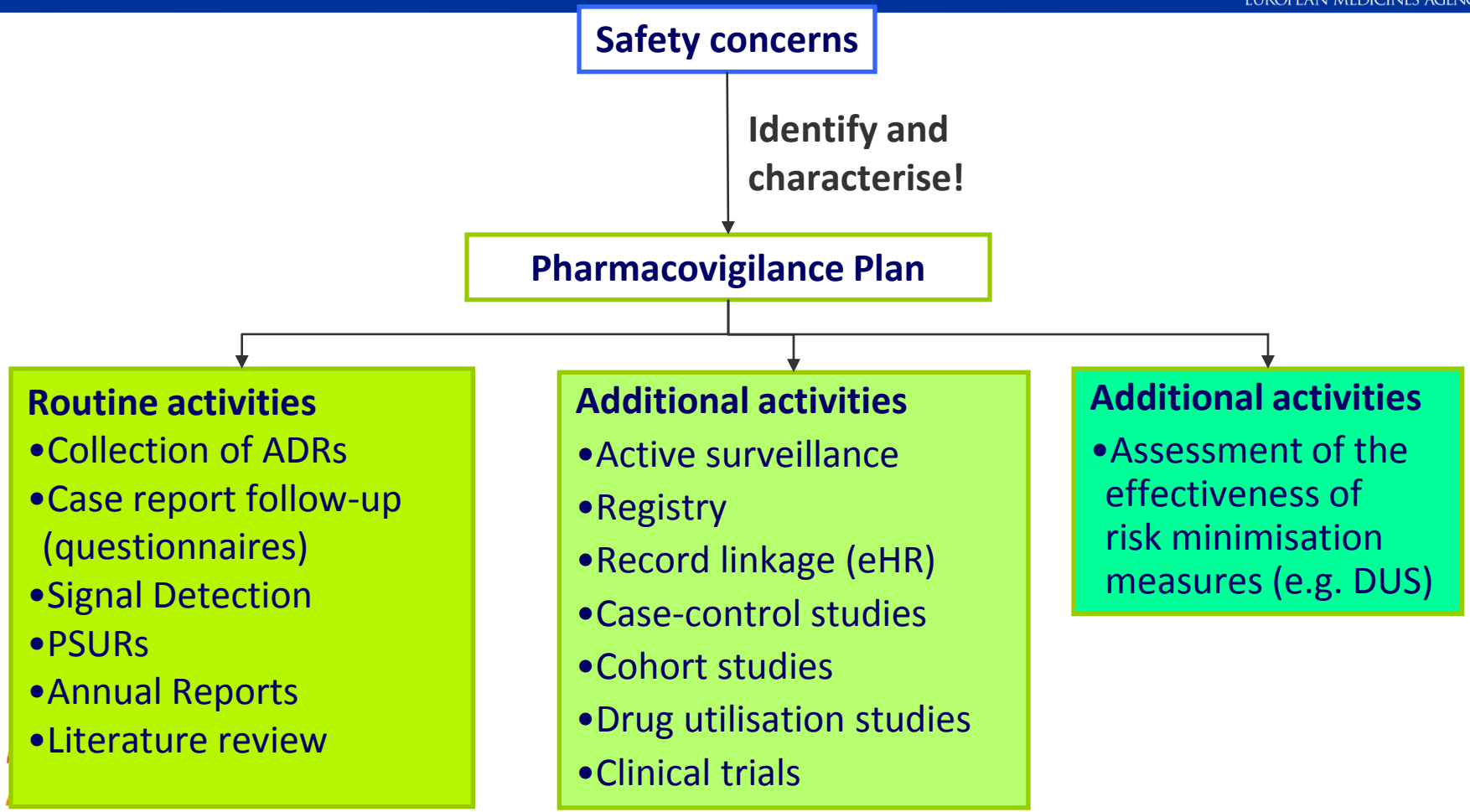
Part I		Product(s) overview
Part II		Safety specification
	Module SI	Epidemiology of the indication(s) and target population(s)
	Module SII	Non-clinical part of the safety specification
	Module SIII	Clinical trial exposure
	Module SIV	Populations not studied in clinical trials
	Module SV	Post-authorisation experience
	Module SVI	Additional EU requirements for the safety specification
	Module SVII	Identified and potential risks
	Module SVIII	Summary of the safety concerns
Part III		Pharmacovigilance plan
Part IV		Plans for post-authorisation efficacy studies
Part V		Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
Part VI		Summary of the risk management plan
Part VII		Annexes


Safety Specification
Identify:
What is known!
What is not known?
Drug
Target population
Disease
•Pharmacodynamics
•Pharmacokinetics
•How will it be used?
•Adverse event profile
•Class effects?
•Interactions?
•Level of confidence?
•Who was studied?
•Who wasn't studied?
•Risk factors?
•What events can we expect in this population?
•Natural history
•Epidemiology
•What events occur as part of disease?
Important identified risks
Important potential risks
Missing information
Safety concerns

Example: Lenvima

Safety concerns

Summary of safety concerns	
Important identified risks	Hypertension Proteinuria Renal failure or impairment Hypokalaemia Cardiac failure Posterior reversible encephalopathy syndrome (PRES) Hepatotoxicity Hemorrhagic events Arterial thromboembolic events (ATEs) QTc prolongation
	Hypocalcemia
Important potential risks	Gastrointestinal perforation and fistula formation Venous thromboembolic events (VTEs) Abnormal pregnancy outcome, excretion of lenvatinib in milk Male and female fertility Pancreatitis Bone and teeth abnormalities in the pediatric population Impaired wound healing Interstitial Lung Disease (ILD)-like conditions Potential of lenvatinib for induction/inhibition of CYP-3A4 mediated drug metabolism
Missing information	Use in the pediatric population Use in severe hepatic impairment Use in severe renal impairment Use in patients from ethnic origins other than Caucasian or Asian Use in patients aged ≥ 75 years


Safety concerns
Identify and characterise!
Pharmacovigilance Plan
Routine activities
•Collection of ADRs
•Case report follow-up (questionnaires)
•Signal Detection
•PSURs
•Annual Reports
•Literature review
Additional activities
•Active surveillance
•Registry
•Record linkage (eHR)
•Case-control studies
•Cohort studies
•Drug utilisation studies
•Clinical trials
Additional activities
•Assessment of the effectiveness of risk minimisation measures (e.g. DUS)

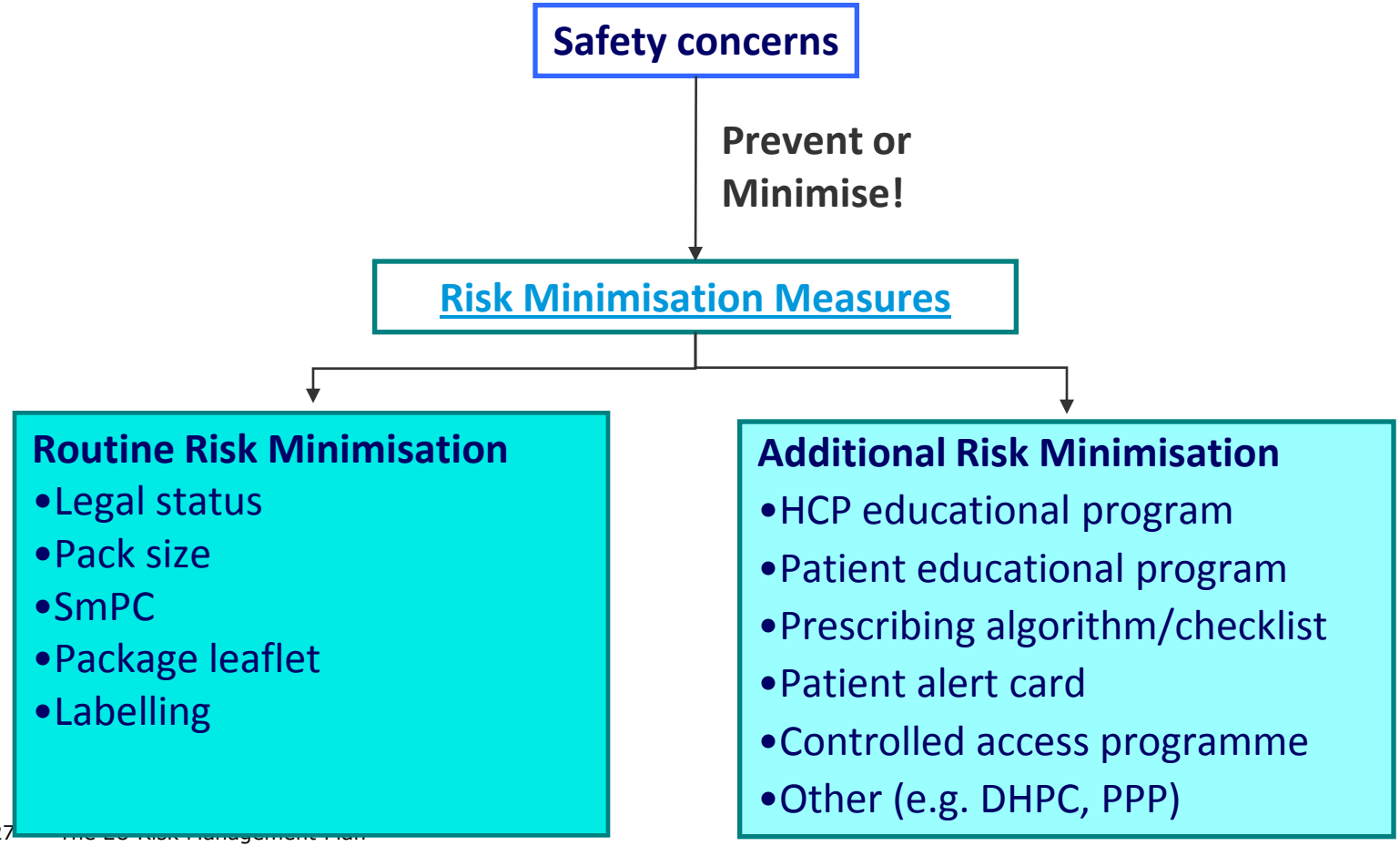
Additional pharmacovigilance activities

- **Active surveillance**
  - Sentinel sites
  - Intensive monitoring schemes
  - Prescription Event Monitoring (PEM)
  - Registry
- **Observational studies (non-interventional)**
  - Cross-sectional studies (Surveys)
  - Cohort studies
  - Case-control studies
  - Case series
  - Case cross-over
  - Case-time-control study
  - Drug Utilisation Study (DUS)
- **Pre-clinical and clinical studies (interventional)**
  - PK/PD studies
  - Drug interaction studies
  - Randomised Controlled Trial (RCT)
  - Large Simple Trial

Pharmacovigilance Plan

Description of pharmacovigilance activities:

- Routine activities beyond signal detection and PSUR
- Additional activities: PASS Summaries
  - Study title
  - Rationale and study objectives
  - Study design
  - Study populations
  - Milestones


Safety concerns
Prevent or Minimise!
Risk Minimisation Measures
Routine Risk Minimisation
•Legal status
•Pack size
•SmPC
•Package leaflet
•Labelling
Additional Risk Minimisation
•HCP educational program
•Patient educational program
•Prescribing algorithm/checklist
•Patient alert card
•Controlled access programme
•Other (e.g. DHPC, PPP)

Routine Risk Minimisation Measures

- ✓ **Summary of Product Characteristics** (SmPC)
- ✓ **Product information** (PIL)
- ✓ **Pack size** (controlling the number of dosage units)
  - Limited validity/size of prescription
- ✓ **Legal status** of medicine (defined in Annex II.B as conditions or restrictions for supply or use of medicinal product)
  - Restricted medical prescription (e.g. administration in hospital only)
  - Special medical prescription (e.g. for narcotic or psychotropic substances; potential for addiction, abuse or use for illegal purposes)

Additional Risk Minimisation Measures

- ✓ **Health Care Professional Educational Programme**
  - Dear Health Care Professional Letter
  - Physician's guide to prescribing
  - Pharmacist's guide to dispensing
  - Algorithm/checklist before prescribing/dispensing
  - Specific training programme
- ✓ **Patient Educational Programme**
  - Patient Alert Card
  - Patient Reminder Card
  - Patient Information Brochure/Booklet
- ✓ **Controlled access programme**
- ✓ Other (e.g. pregnancy prevention programme)

EU-specific Aspects of Risk Minimisation

In EU, risk minimisation activities (e.g. restricted access, educational programmes, control of prescription, named patients registries) depend in many cases on national legislation

Principles applied at CHMP Opinion:

- ✓ Only **key components of educational material** considered essential for the safe use of the product are adopted
- ✓ Obligation (MAH/MS) to implement components, but practical aspects may differ across Member States
- ✓ No marketing in Member States without implementation
- ✓ Educational programme must not be promotional
- ✓ Agreement on **key message(s)** of educational programme; details left to National decision

Effectiveness of Risk Minimisation

Effectiveness of risk minimisation activities should be **measured**

- Legislation requires **active monitoring of the outcome** of risk minimisation measures
- Essential aspect of continuous pharmacovigilance
- Criteria to assess the effectiveness of each (additional) risk minimisation activity should be **outcome measures** that **indicate the success or failure** of the process implemented based on agreed standards
- Measurement of effectiveness is an additional pharmacovigilance activity of the RMP with defined milestones at regular intervals
- Consider burden on patients/prescribers and performance in healthcare system

Measuring the Effectiveness of Risk Minimisation Activities

- Periodic market research studies (**surveys**) among prescribers on awareness of risks/precautions using validated questionnaires
    - E.g. the success of a hepatic surveillance plan was measured by 6-monthly prescriber surveys until adequate levels of awareness and understanding have been obtained (measure clinical actions, not only knowledge!)
- Retrospective analysis of large prescription databases (**PASS, Drug Utilisation Study**) to compare ADRs pre/post implementation or to detect level of off-label/misuse (final outcome measure: incidence)
- Retrospective analysis of **spontaneous ADRs** to measure ADR frequencies pre/post implementation. BUT may not be reliable if risk has a high background incidence in exposed population

Conclusion

RMP is an essential tool to manage the risk throughout the lifecycle of a medicinal product

PRAC has now experience of 3 years in assessing RMPs

Gathered evidence to update the guidance, focus on prospective planning:

- Better use of post-marketing tools for monitoring the benefit/risk balance of the product (e.g. PSUR)
- Reposition RMPs as a value added tool early in the lifecycle, supporting safe innovation and actual management of risk.

Thank you for your attention

Further information

Emil.Cochino@ema.europa.eu

European Medicines Agency
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

Follow us on **@EMA_News**