SCOPE Joint Action
Stakeholder Event

SCOPE Work Package 5
Signal Management
Introduction

20 – 21 March 2017
London

Contents of this session

Signal Management highlights for industry

- Signal detection and management
- Validation and assessment
- Prioritisation

Work Package 5 – Signal Management

WP 5 – Best practice in signal management within the network of National Competent Authorities (NCAs)

- *Make the best use of the currently available tools*
- *Not replace current legislation, but go one step further*
- *Focus on practical aspects and challenges at NCA level*
- *Recommendations for future enhancements that would benefit the whole EU regulatory network*

SIGNAL DETECTION AND MANAGEMENT

EU legislation

EU legislation for signal management

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities

Terminology Challenges

MS level
CIOMS VIII

- ‘Signal verified’ as a signal of suspected causality
- SOP/instructions at national level might describe ‘how signal prioritization and evaluation are approached’
- Prioritization is a continuous process performed at every step
- ‘Signal evaluation’ varies in extension and can be similar to thorough signal assessment

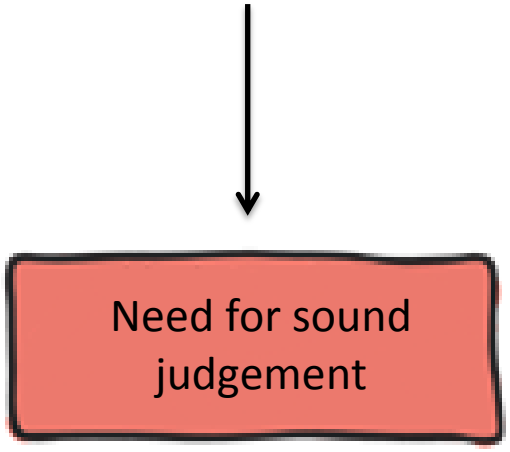
EU level
IR / GVP

- Introduces ‘signal confirmation’ as a procedural step in EPITT
- Prioritization is the responsibility of the PRAC
- Signal assessment might seem duplication of work

Important Aspects of Signal Management

All activities in signal management take place in the presence of some level of uncertainty

- Completeness and strength of the data
- Evidence from different sources, different nature, different weight
- Accumulated and gathered over time

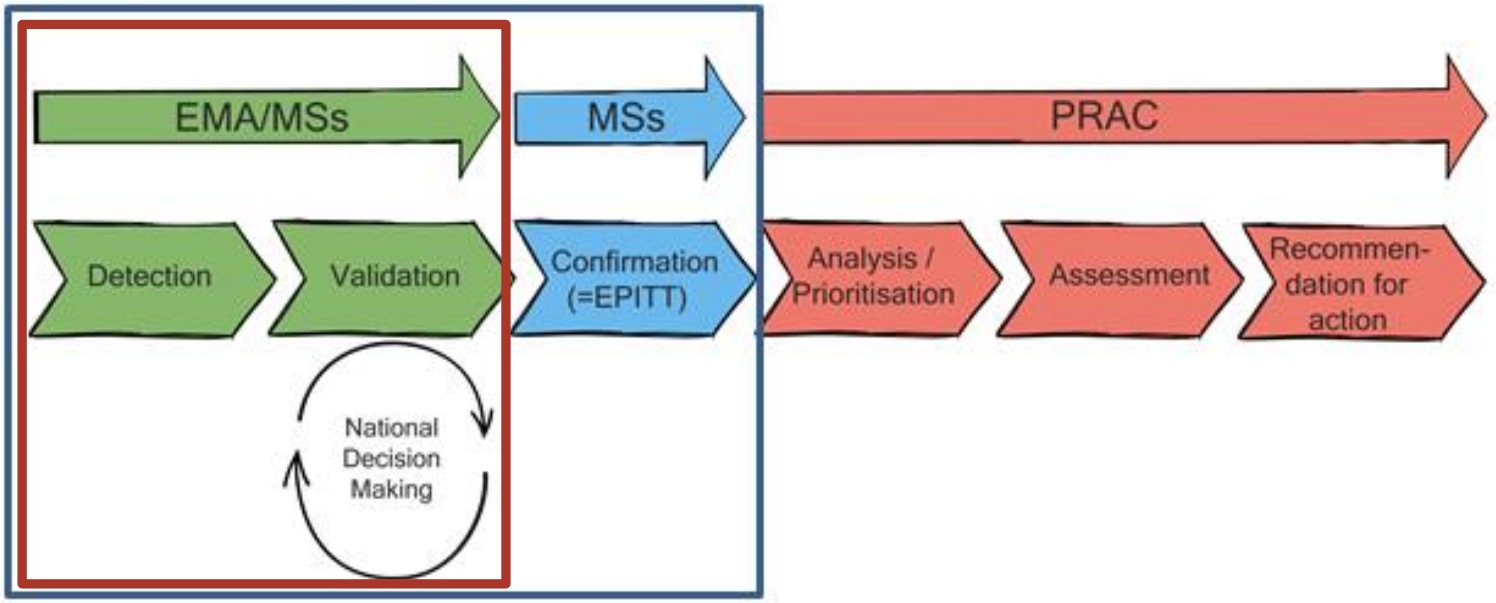


GVP Impact

- Number of areas of confusion for NCAs under the existing GVP
- SCOPE worked closely with EMA to clarify responsibilities in latest draft
  - Foster heterogeneity in signal detection at national level
  - Promote consistency in validation, confirmation, tracking
  - Clarify boundaries between national and EU processes

Signal Management

- Signal management as provided in the legislation



Equally applicable to industry

eRMR Guidance

Not specifically covered through SCOPE as guidance was under development by the EMA

- Access during Q4 2017 subject to EMA Management Board Announcement/ Audit
- MAH access to EVDAS (following registration)
- Line listing and ICSR Form - subject to access policy
- '*Screening for adverse reactions in EudraVigilance*'

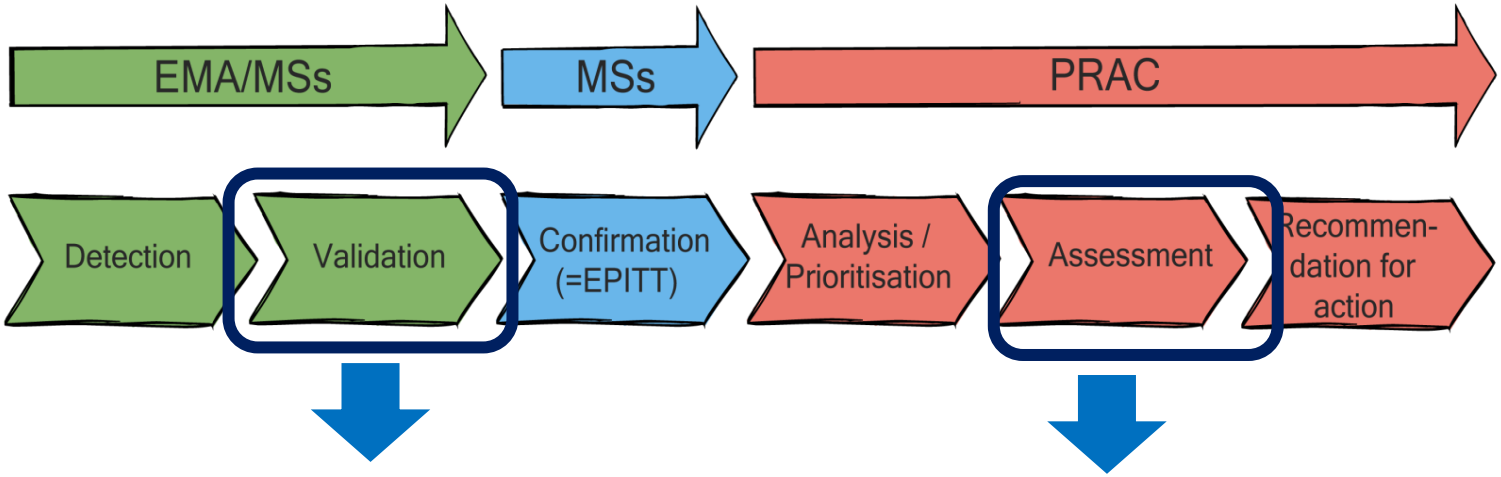
MAH's involvement

When should NCAs involve MAH's in early signal management?

- ✓ For national issues, at MS's own discretion
- ✓ At first review step or when additional information is needed
- ✓ If signal is detected, but not enough information available for validation

SIGNAL VALIDATION AND ASSESSMENT

Signal management process



Both involve ***evaluation of the evidence supporting the signal***

Signal Validation

Evaluation of the data

Aim: deciding if further analysis necessary

Focus: New information? Reasonable possibility?

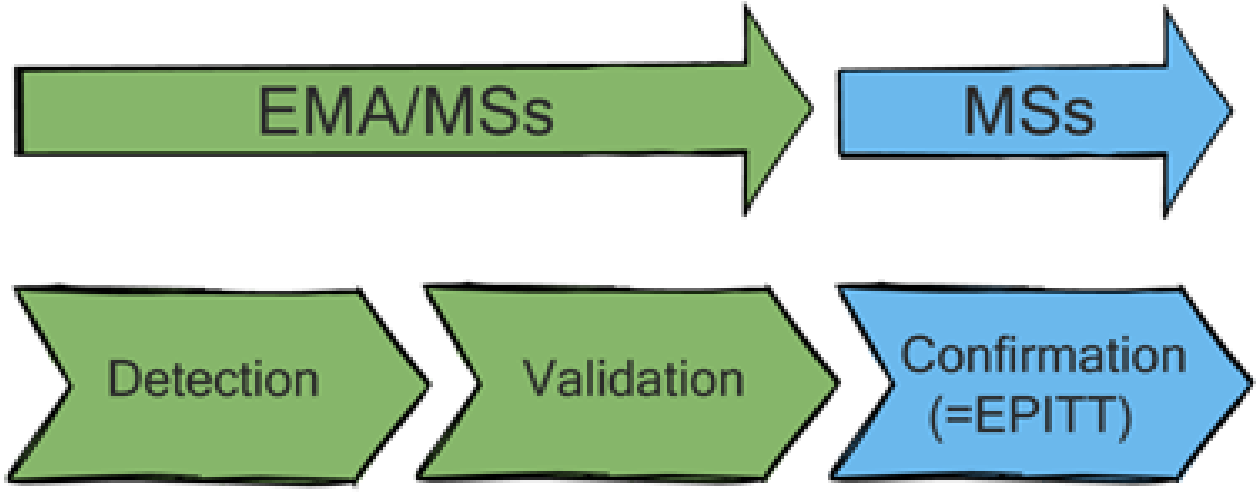
Minimum: Signal is not based on **duplicates** and there is a plausible **time to onset**

Depending on organizational structure and possibilities

- More extensive evaluation (signal assessment)
- Multidisciplinary teams involved (internal/external expertise)
- Proposal for regulatory action (additional PhV or RMM)

Signal validation process

From signal detection to signal validation



A **detected signal** that justifies <u>verificatory action</u>

A **validated signal** that justifies <u>further analysis</u>

Signal Assessment

- Performed by **PRAC Rapporteur** or **Lead Member State**
  If several products involved, Rapporteur appointed by PRAC
- Evaluation of data
  - Initial data that generated the signal
  - New data (**cumulative review**)
- Sources of information
  - Application dossier
  - Literature
  - Spontaneous reports
  - Expert consultation
  - …

Challenge → *Only overall, high-level guidance on legislation*

Signal Validation vs Signal Assessment

Validation

EMA/MS/MAH

Usually quicker and less extensive
Based on initial data that generated the signal
Aim: deciding if further data/analysis is necessary
Focus: new information? reasonable possibility?
Outcome: enter a signal in EPITT (or not)

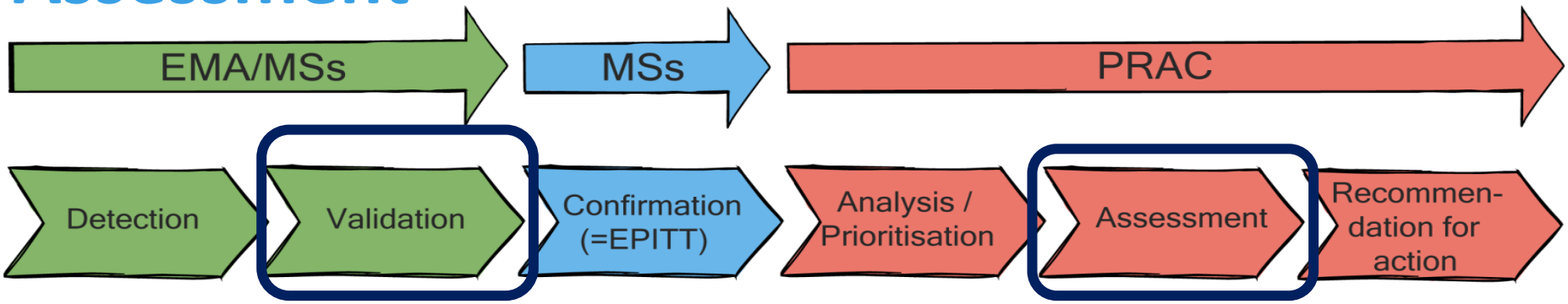
Assessment

PRAC Rapporteur / Lead Member State (With MAH input)

More extensive and thorough assessment
More data available for assessment
Aim: decide on regulatory action
Focus: definitive conclusion on causal association
Outcome: take a regulatory action (or not)

But they both involve evaluation of data

Signal Validation and Assessment



- ✓ Signal validation and signal assessment are different steps in signal management process, both involving evaluation of data
- ✓ They are different in the type of data to evaluate, in their aim, focus, and outcome
- ✓ A checklist can be useful for a consistent approach between different MSs
- ✓ It is important to know the roles of MSs, EMA and PRAC in each one of the steps

PRIORITISATION

prioritize (praɪˈɒrɪˌtaɪz) *or* prioritise

vb (*tr*)

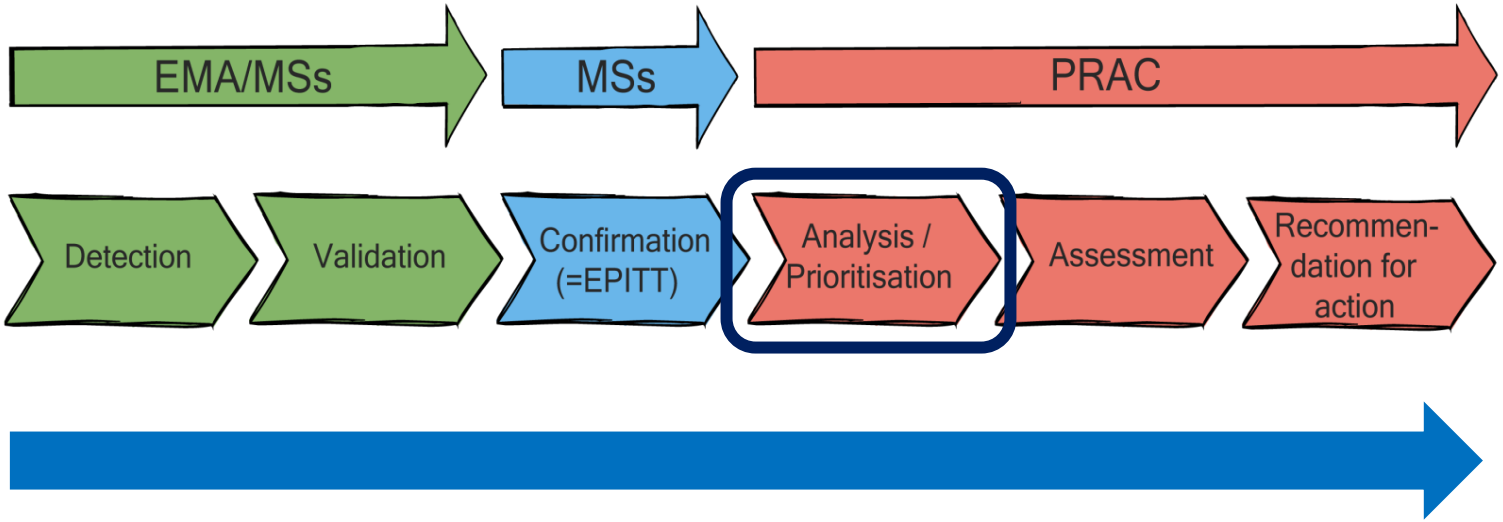
1. to arrange (items to be attended to) in order of their relative importance

2. to give priority to or establish as a priority

ˌprioritiˈzation, **ˌprioritiˈsation** *n*

"CITE" Collins English Dictionary – Complete and Unabridged, 12th Edition 2014 © HarperCollins Publishers 1991, 1994, 1998, 2000, 2003, 2006, 2007, 2009, 2011, 2014

Who prioritises?



All actors in the signal management process carry out prioritisation

When do we prioritise?

Current GVP IX

- An additional step in the signal management process
- Administrative task to establish legal/ procedural timetables for assessment

SCOPE Best Practice

- An ongoing process throughout the signal management process
- Scientific reasoning undertaken for:
  - Health impact
  - Resourcing
  - Time scheduling

Why use systematic tools?

- Aid to the management of **multiple dynamic issues** in the allocation of resources
- Ensures that **appropriate timescales** are defined to meet MSs public health and other obligations
- Aid to pharmacovigilance **audit**
- Improve **consistency** between assessor recommendations

Available tools

Prioritization tools can help to reduce the subjectivity of prioritization process and increase standardization

- Levitan et al, 2008: prioritization tool developed and tested in a MAH database
- FDA 2012: Draft guidance for Classifying Significant Postmarketing Drug Safety Issues. Validation and implementation unknown
- MHRA 2013: Regulatory Pharmacovigilance Prioritisation System (RPPS)

Take home messages

- Prioritisation happens at every step of the signal management process, and is a continual activity
- We can use tools to reduce the subjectivity of reliance on individual judgment
- It is important to consider the following themes:
  - Public health implications
  - Strength of evidence
  - NCA obligations
  - Public perceptions

Questions?

Contact:

scope@mhra.gsi.gov.uk