Facts

- 121 medecines were withdrawn
  for safety reasons in the last 40 years
- 33% within 2 years of marketing
- 50% 5
- ADRs accounted for > 100 000 deaths
  in the USA, in the last 10 years …

RISK EVALUATION AND RISK MANAGEMENT

Daniel Brasseur

Brussels 24 October 2006

CONTENT

- Applications for marketing authorisation for medicinal products
- Risk management system
- Risk evaluation
- Post marketing follow up
- Roles and responsibilities
  - Applicant/Marketing Authorisation Holder
  - Member States
  - EMEA
  - European Commission
- Points for reflection

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Application

- Definition of risk for medicinal products *“Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients’ health or public health or animal health”*
- Content of an application for marketing authorisation Quality, Safety, Efficacy data
-

Application

- Definition of risk for medicinal products *"Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health or animal health"*
- Content of an application for marketing authorisation Quality, Safety, Efficacy data
- *"shall be accompanied by a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce"*

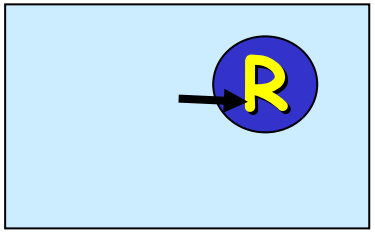
Article 8 (3)(ia) of Directive 2001/83/EC

Risk Management Pillars

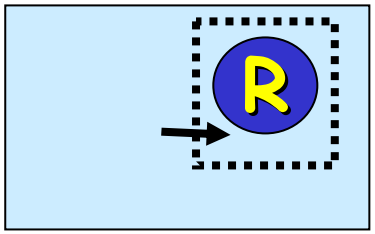
- Detection
- Identification
- Evaluation acceptable risk vs. benefit
- Minimisation and effectiveness of measures
- Communication on the product information and additional information

Risk ?

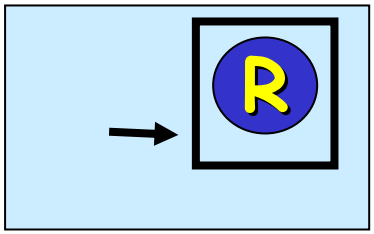
Identify
- Detect



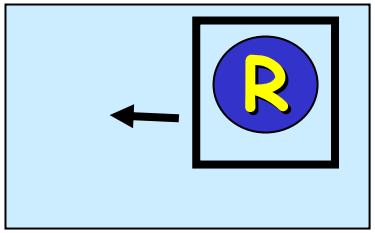
Define
-Assess
-Delimit



Minimize
- Manage



Communicate
- Monitor



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Risk Management System

- Procedures and activities designed to identify, characterise, prevent or minimise risks associated with medicinal products
- Assessment of the effectiveness of risk minimisation interventions
- Carried out by applicant/marketing authorisation holder
- Evaluation by the competent authority

- Requested for
  - New medicinal products
  - Extensions
  - Upon request of competent authorities
  - Upon availability of new relevant data
  - For class related issues

Risk Management Plan

- Safety specifications
- Pharmacovigilance plan
- Risk minimisation plan

The EU Risk Management Plan

Part I

- **Safety Specification**
- **Pharmacovigilance Plan**

} **ICH E2E**

Part II

- **Evaluation of the need for risk minimisation activities,**

if a need for additional activities

- **Risk minimisation plan**

- Safety specifications
  - Non-clinical (toxicity, general pharmacology, drug interaction, etc)
  - Clinical (safety database, populations not studied, adverse events, adverse drug reactions, interactions, epidemiology, etc)
  - Potential for medication errors, abuse/misuse, off label use
  - Important identified risks, potential risks, missing information

Pre-Clinical Safety Assessment

- In Vitro models (cells, tissues…)
  - Development of mechanistic models
  - Validation (Reproducibility, reliability)
  - Predictibility
- In Vivo models (Animals)
  - Avoiding (Replacing, reducing, refining)
  - Transferability (Extrapolation to humans)
  - Predictibility (Duration/Dose levels)

- Safety specifications
  - Non-clinical (toxicity, general pharmacology, drug interaction, etc)
  - Clinical (safety database, populations not studied, adverse events, adverse drug reactions, interactions, epidemiology, etc)
  - Potential for medication errors, abuse/misuse, off label use
  - Important identified risks, potential risks, missing information

Other ADRs which are unlikely to be found in clinical trials

- adrs which have a long latency
- adrs which need prolonged exposure
- adrs due to cumulative effects
- adrs which are rare
- adrs which mimic common diseases

Numbers of exposed patients needed to detect adrs

Incidence of adr to be detected	Spontaneous background incidence	*Minimum* number of patients
1 in 100	1 in 10,000 1 in 1,000 1 in 100	520 730 2,000
1 in 500	1 in 10,000 1 in 1,000 1 in 100	3,200 6,700 35,900
1 in 1,000	1 in 10,000 1 in 1,000 1 in 100	7,300 20,300 136,400
1 in 5,000	1 in 10,000 1 in 1,000 1 in 100	67,400 363,000 3,255,000

Safety Aspects Systematically looked for during Drug Development

- QT prolongation
- Liver, / Renal, / Bone Marrow toxicity
- Drug-drug interaction
- Polymorphic metabolism

- Pharmacovigilance plan
  - Based on safety specifications
  - To be submitted at the time of applications and when post-marketing safety issues arise
  - Should address
    - Routine pharmacovigilance practices
    - Additional pharmacovigilance activities/action plan
    - Actions to be completed/milestones

- Risk minimisation plan
  - Risk minimisation action for each safety issue appearing in a list
  - Discussion on the risk minimisation **actions**
    - Objective of the action
    - Rational
    - Monitoring by marketing authorisation holder
    - Assessment of the effectiveness of the action
    - Milestones for evaluation and reporting
  - Can be appended to the Periodic Safety Update Report

Summary of activities in EU-RMP

Safety concern	PhV Plan	Risk Min Activities
1. **Hepatitis**	• Routine PhV. • Study to investigate the incidence and risk factors for hepatitis in Wonder drug and other immunosuppressant drugs using GPRD database	• Contraindication for patients with active viral hepatitis in section 4.3 of the SPC • Warning in section 4.4 of the SPC • Listed as ADR in section 4.8 • Educational pack for GPs

Guideline on risk management system

- Has been published
- Is applicable
- Need for more experience
- Need of specialised expertise (pharmacovigilance, epidemiology, risk management, etc)

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL PRODUCTS FOR HUMAN USE

DRAFT AGREED BY PhVWP	26 July 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	27 July 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	5 October 2005
ADOPTION BY CHMP	14 November 2005
DATE FOR COMING INTO EFFECT	20 November 2005

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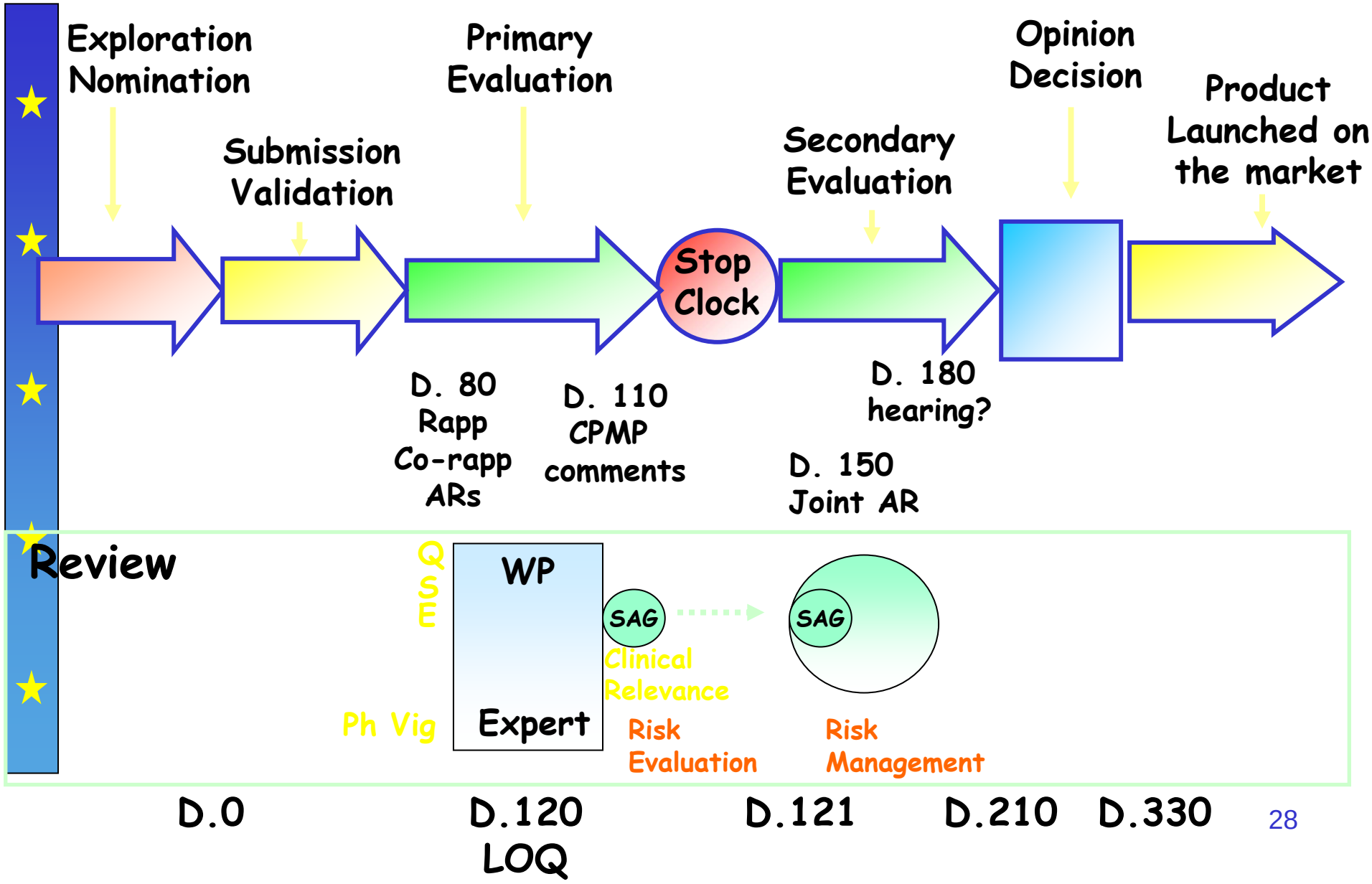
Risk evaluation

- The evaluation system in the EU
  - Centralised procedures
    - CHMP opinions
    - EC decision valid in all Member States
  - National procedures
    - Via decentralised/mutual recognition
    - Purely national
    - Decision by the Member States concerned


Exploration
Nomination
Submission
Validation
Primary
Evaluation
Stop
Clock
Secondary
Evaluation
Opinion
Decision
Product
Launched on
the market
D. 80
Rapp
Co-rapp
ARs
D. 110
CPMP
comments
D. 180
hearing?
D. 150
Joint AR
Review
Q
S
E
WP
Expert
Ph Vig
SAG
Clinical
Relevance
Risk
Evaluation
SAG
Risk
Management
D.0
D.120
LOQ
D.121
D.210
D.330

- Referrals for Community interest
  - CHMP opinions
  - EC decision
  - To be applied by the Member States concerned
- Evaluation of the risk management system
  - By the EMEA for centrally authorised products
  - By the Reference Member State for nationally authorised products via decentralised/mutual recognition
  - By the Member States for purely national products

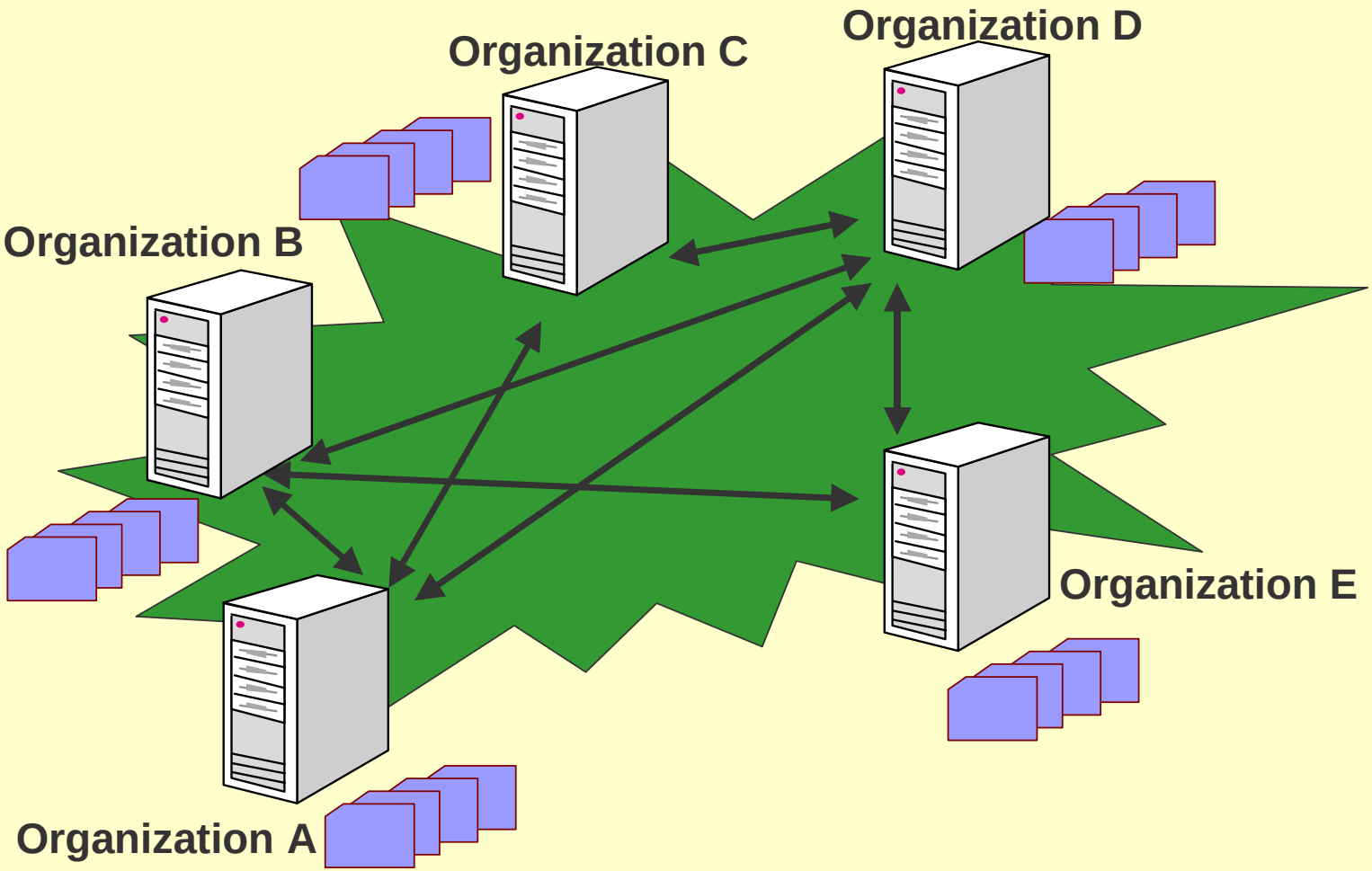
Post-marketing follow-up

- Pharmacovigilance at national level
- Coordination by the EMEA
- Decision making process
  - EC for centrally authorised products
  - EC+Member States for referrals
  - Member States for other decisions

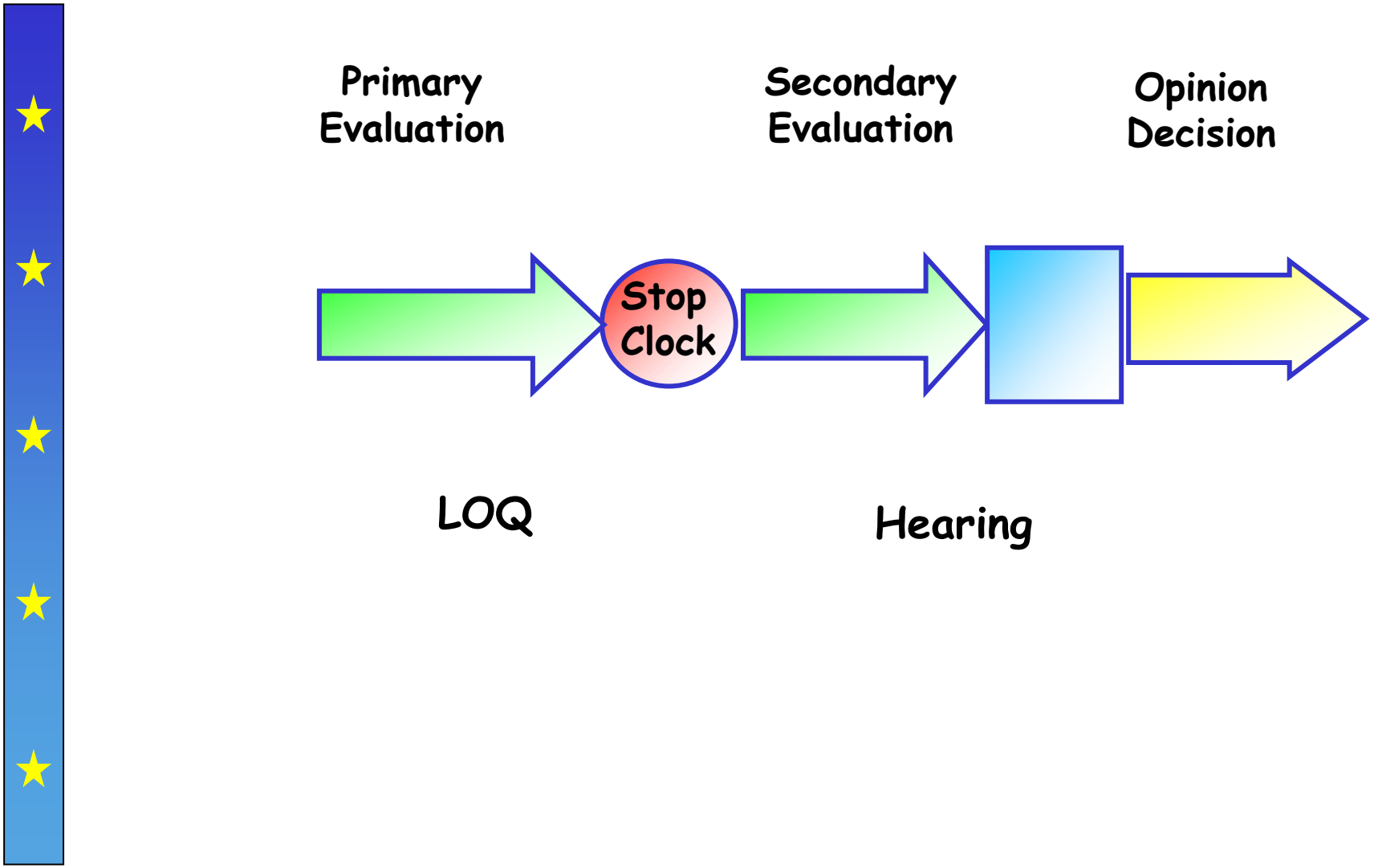
- Procedures in place
  - Rapid alert (Member States/EMEA/EC)
    - Quality defect
    - Pharmacovigilance/safety concern (change B/R, unexpected serious adverse reactions, expected but greater rate, evidence from clinical trials, greater risk vs. alternatives)
  - Reponses
    - Urgent safety restriction
    - Suspension/revocation with or without recall
    - Changes in the information
    - Interim measures

The Reality

Message Routing



- Specific tools
  - For centrally authorised products in case of **urgent** action needed
    - Opinion of the CHMP
    - Provisional measures adopted by EC
    - EC final decision
  - Member States may suspend (on their own/at the EC request) the use of a centrally authorised product
    - Evaluation by the CHMP
    - EC decision


Primary Evaluation
Secondary Evaluation
Opinion Decision
Stop Clock
LOQ
Hearing

– Member States may suspend, revoke, vary the marketing authorisation of nationally authorised products on pharmacovigilance grounds provided information is sent to

- The EMEA
- Other Member States
- The marketing authorisation holder

– Where urgent action is needed Member States may suspend the marketing authorisation provided information is sent to
  - The EMEA
  - EC
  - Other Member States
– Opinion of the CHMP **mandatory** in case of suspension/revocation and *optional* for variations

Article 107

- EC can impose temporary measures in all Member States
- Final measures with EC decision

- Other tools
  - Financial penalties for non-compliance
  - Inspections of the marketing authorisation holder premises
  - Inspection related to pharmacovigilance

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Roles and responsibilities

- Applicant/marketing authorisation holder
  - Pharmacovigilance system
  - Risk management system
  - Reports on suspected adverse reactions
  - Eudravigilance reporting obligations
  - Periodic safety updated reports
  - Maintenance of the marketing authorisation

- Member States
  - National pharmacovigilance system
  - Inform EC/EMEA/other Member States on actions taken
  - Fulfil of Eudravigilance reporting obligations
  - Implement of EC decisions

- EMEA
  - Close cooperation with national pharmacovigilance systems
  - Coordination of evaluation
  - Maintenance Eudravigilance database
  - Monitoring legal obligations of marketing authorisation holders
  - Rapporteur evaluation on behalf of the CHMP
  - Communication of CHMP opinions to the EC

- EC
  - Decisions for centrally authorised product and referrals
  - Temporary decisions for all products

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Points for reflection

- From national decisions to decisions based on cooperation mechanisms
  - EC decision/national expertise
  - National decision/decentralised procedure
  - National competence vs. EU competence
  - Coordination in case of urgency or crisis
  - National decisions but EU coordination with embargo

- From national decisions to decision making process influenced by
  - International information
  - National policy
  - Harmonisation mechanisms
  - Patients and health care professionals
  - Transparency processes

- From “fixed” decisions to a “continuum”
  - Follow-up measures
  - Conditions to be fulfilled
  - Modifications of the risk management plan
  - Permanent involvement of the cooperation system

- From “stability” of the marketing authorisation to modifications

  – Permanent evaluation of the B/R
  – More transparency on new data
  – More transparency on the clinical trials
  – More dialogue with stakeholders

- What about divergent positions between risk evaluation and risk management?
- What about divergent position between scientific evaluation and decision to be taken by the Commission?
- What are other criteria that the Commission should take into account for the final decision?

CONCLUSIONS

- Several actors
- Borderline/Limits between risk evaluation and risk management not always clear-cut
- Roles and responsibilities to be clearly defined in all cases
- Strong network is needed
- Transparency is a key element

"The use of the Foxglove is getting abroad and it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable."

William Withering 1785

Thank you