



IRISH MEDICINES BOARD

Implementing the New Pharmacovigilance Legislation

Irish Medicines Board, Pharmacovigilance Information Day, Dec 2011

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Implementation Planning and Deliverables

New Legislation:

- Why? Promote and protect public health – effective risk minimisation and optimisation of use of medicines
- What? Regulation (EU) No. 1235/2010 and Directive 2010/84/EU
- When? By July 2012, some later.
- **How? Implementing Measures, Good Vigilance Practice** but also **new processes, existing processes to be amended**, new IT tools/functionalities to be developed and implemented.
- Focus on consensus building and collaboration to support a **harmonised approach** to implementation across the EU network.



Scope of Changes

- Authorisation requirements
- Risk Management Plans
- Post-Authorisation Studies (Safety and Efficacy)
- Effectiveness of risk minimisation
- Adverse Drug Reactions reporting
- Strengthened Signal detection
- Product Information
- Periodic Safety Update Reports
- Scientific Committees / decision-making
- Transparency and communication
- Coordination of inspections
- Pharmacovigilance Audits
- Fees charged and payments for assessments



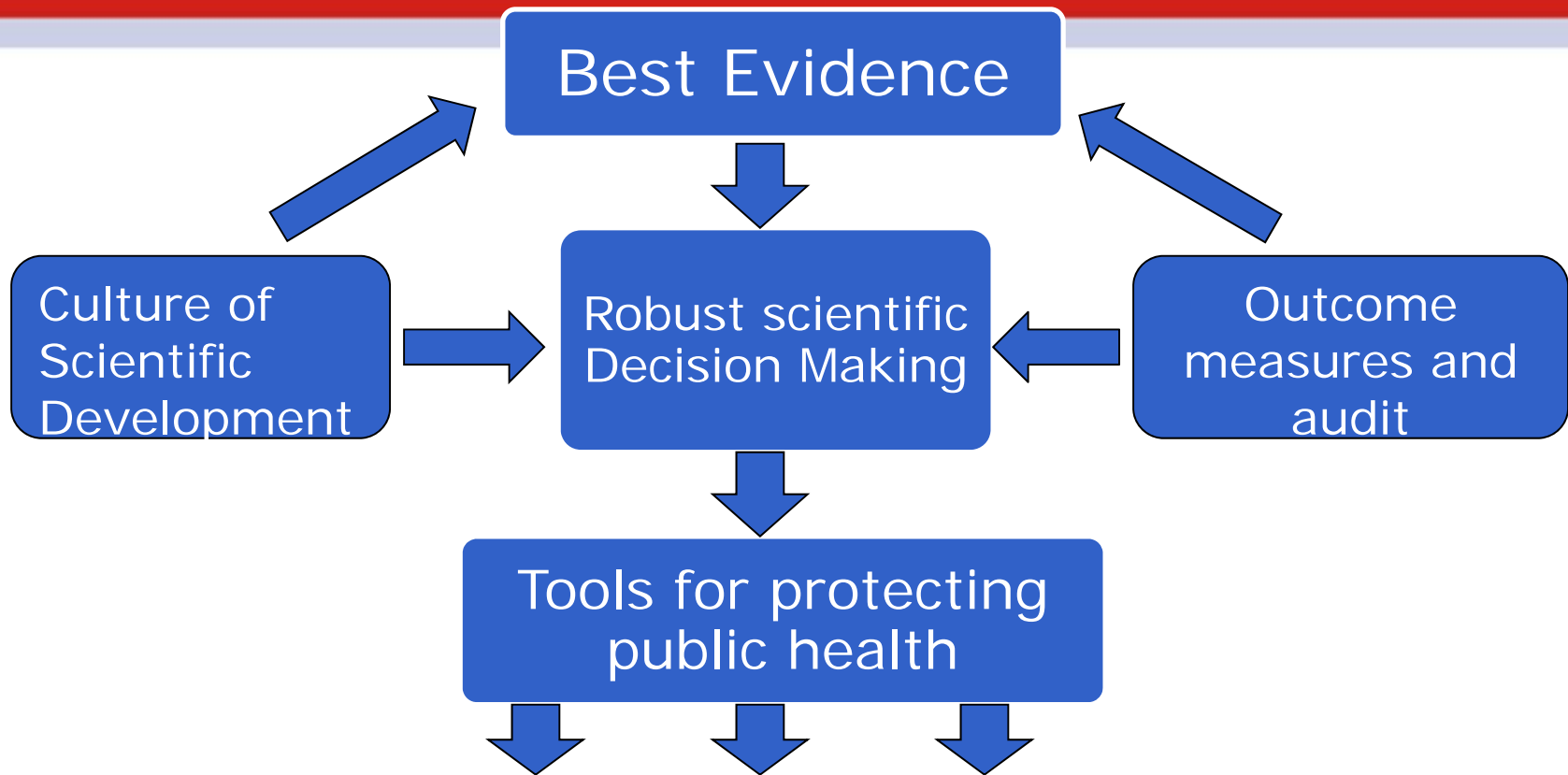
Implementation Planning

Focus is on...

1. Public Health
2. Scientific basis
3. Outcomes
4. Transparency
5. Building Partnerships
6. Rationalisation and Simplification



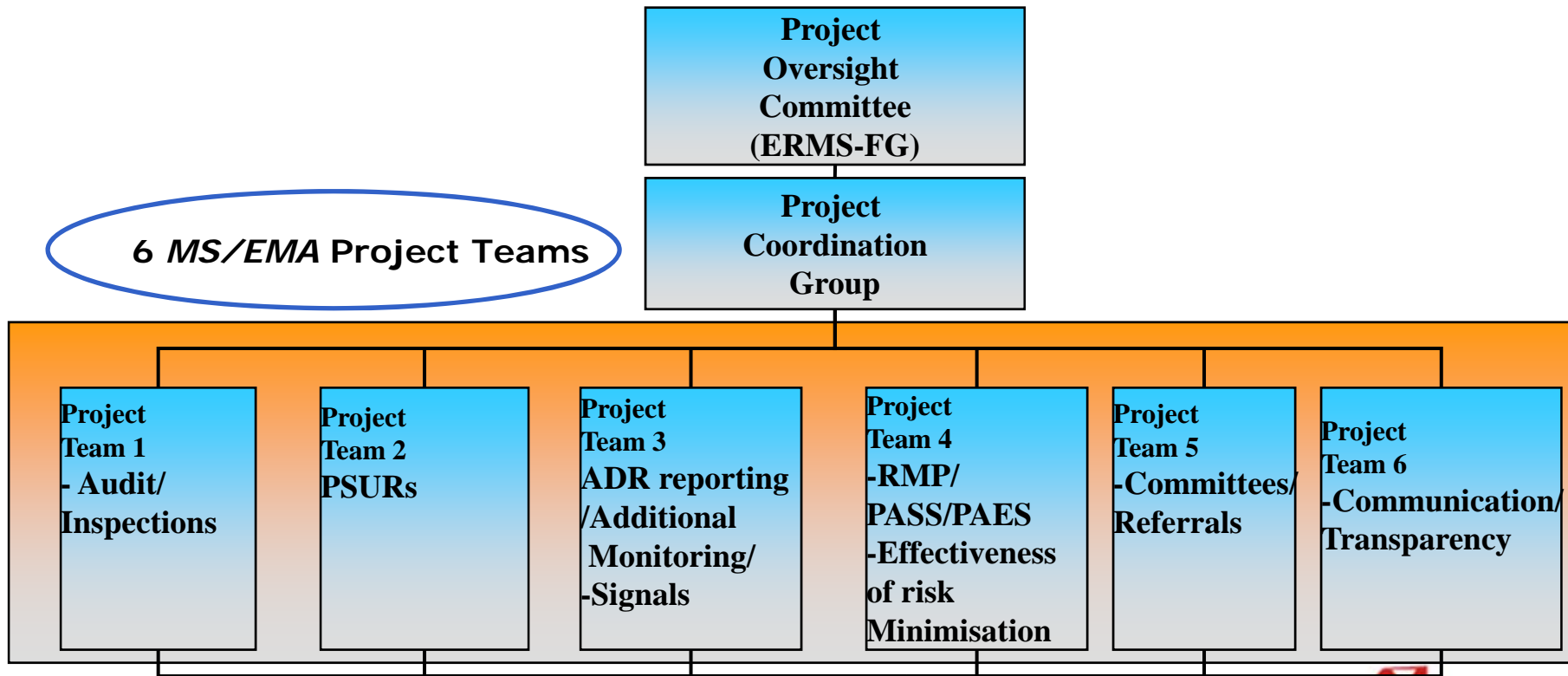
Waller P and Evans S. A model for the future conduct of Pharmacovigilance.
Pharmacoepidemiology and Drug Safety, 2003; 12: 17–29



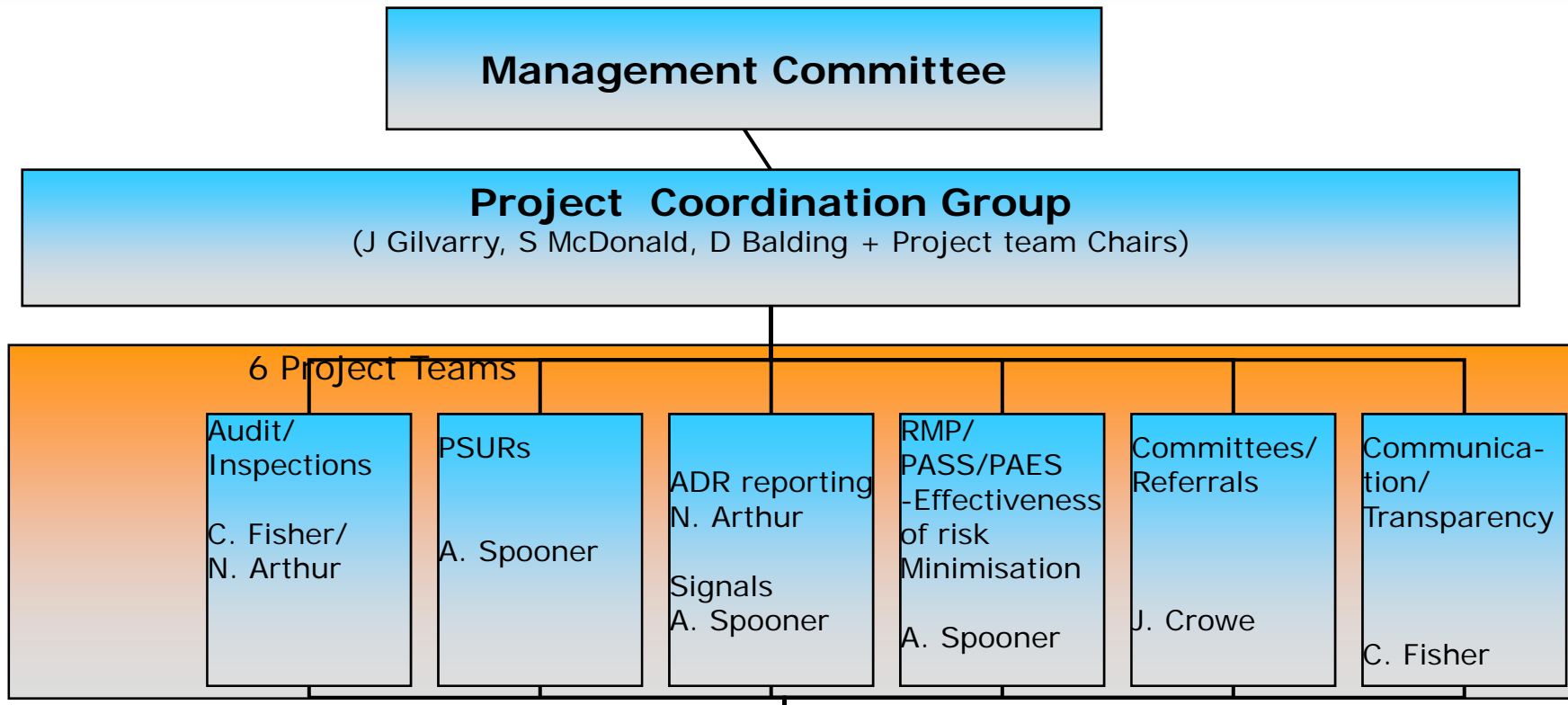
**Measurable performance in terms of
public health benefit**



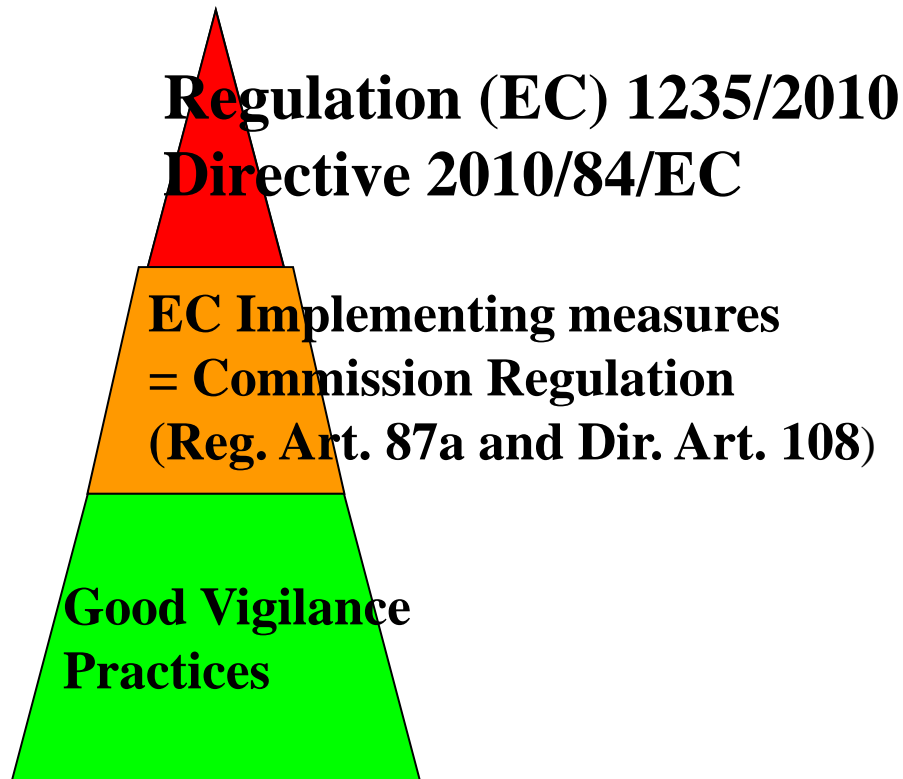
Joint EMA/Member State Implementation Project



IMB PV Legislation Implementation Project – Governance Structure



Implementation Deliverables



Hierarchy of Rules

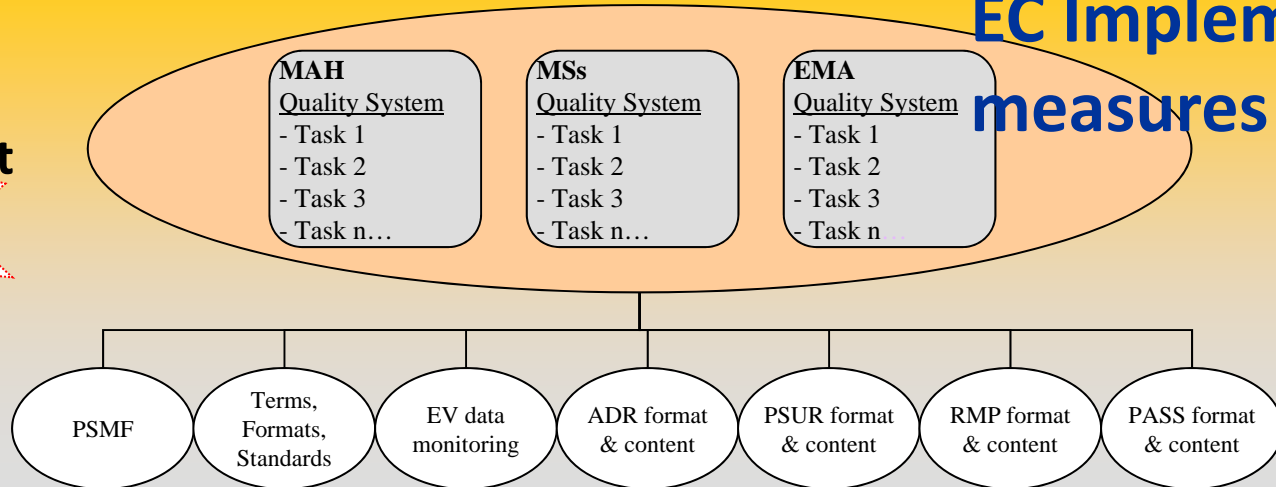
**Implementing
Measures and GVP
will support
harmonised
implementation**



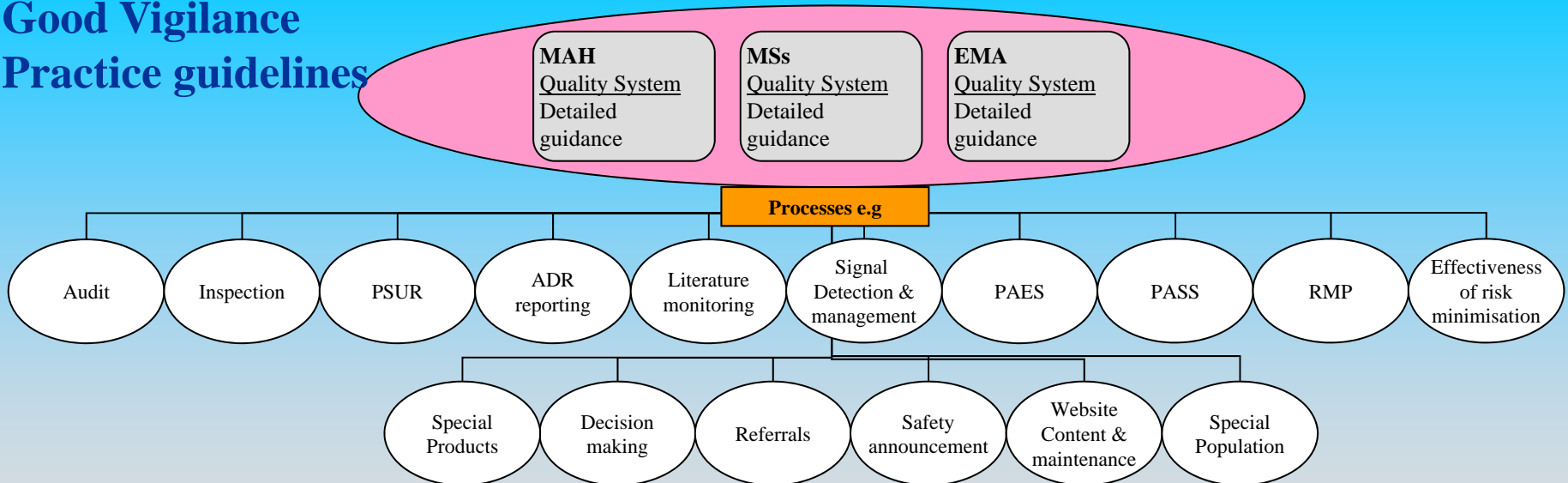
Structure of implementing measures and Good Vigilance Practice: 'GVP'

**Delegated Act
Efficacy
Studies**

**EC Implementing
measures**



**Good Vigilance
Practice guidelines**



Implementing Measures



EMA/Member States technical contribution to EC implementing measures (1/2)

Reg. (EC) 1235/2010 Art. 87a and Dir. 2010/84/EC Art. 108

- (a) The content and maintenance of the **pharmacovigilance system master file** kept by the MAH;
- (b) The minimum requirements for the quality system for the performance of pharmacovigilance activities by the **Agency, the NCAs and MAH**;
- (c) The use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;



EMA/Member States technical contribution to EC implementing measures (2/2)

Reg. (EC) 1235/2010 Art. 87a and Dir. 2010/84/EC

- (d) The minimum requirements for the monitoring of data included in the **EV database** to **determine whether there are new risks or whether risks have changed**;
- (e) The format and content of **electronic transmission of suspected adverse reactions** by MSs and MAHs;
- (f) The **format and content** of electronic **PSURs and RMPs**;
- (g) The **format** of protocols, abstracts and final study reports of the **PASS**;



EC Concept paper on Pharmacovigilance implementing measures

- EC has published a concept paper proposing one global measure
 - Input from the MSs and EMA (technical contribution)
 - Released for consultation on 8th Sept 2011
 - Provides the technical details that will need to be applied when the MSs and EMA implement the new legislation.
 - EC consultation concluded 7th November 2011
 - EC held a Stakeholder day – 22nd November 2011
- Next steps are at European Commission level:
- Discussion with the MSs in the SC
 - Adoption and publication in the official journal



Good Vigilance Practices



Good Vigilance Practices

- Will replace Volume 9A
- Phased development, modular structure.
- First 'wave' of modules (Quality Management System, PVSMF, ICSRs, PSURs, Signals, RMPs, PASS) for publication in **July 2012** with prior public consultation (anticipated end January/**early Feb 2012**).
- Second 'wave' of modules (e.g. Audits, Effectiveness of Risk Minimisation, Communications) to be published in **December 2012** (with prior public consultation).



GVP Development

First 'wave' of modules to be published in July 2012

- Module I: Pharmacovigilance Systems and their Quality Systems
- Module II: Pharmacovigilance System Master File
- Module V: Risk Management Systems
- Module VI: Data Management of Individual Case Safety Reports
- Module VII: Periodic Safety Update Reports
- Module VIII: Post-Authorisation Safety Studies
- Module X: Detection and Management of Signals and information



GVP Development

Second 'wave' of modules to be published in December 2012

- Module III: Pharmacovigilance Inspections
- Module IV: Audits
- Module IX: Post-Authorisation Efficacy Studies
- Module XII: Public Participation in Pharmacovigilance
- Module XIII: Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication

GVP Development

Second 'wave' of modules to be published in December 2012

- Module XIII: Incident Management
- Module XIV: Communication Tools for Pharmacovigilance and Risk Minimisation
- Module XV: Effectiveness of risk Minimisation
- Module XV: Referral Procedures for Safety Reasons



Structure of GVP modules

A – Introduction

B – Structures and processes

C – Operation of the EU network



Key Changes for Marketing Authorisations

- Product Information (black symbol / HCP-patient reporting)
- PhV System Master File (PSMF)
- Renewal
- RMP
- PSURs
- PASS
- Referral

- New Requirements.
- Modification of existing requirements.
- New procedures and decision making.



New requirements

- Black symbol and statements in SmPC and PL for authorised products subject to additional monitoring
- Standard text encouraging HCPs and patients reporting in SmPC and PL for authorised products



Modification of Existing Requirements

- **PSMF on site and PSMF summary in the MA**
 - PSMF summary for MAs authorised after July 2012
 - Introduction of PSMF summary for authorised products before renewal or July 2015 – earlier transition proposed.
 - New format and content (***see presentation from S Curran and M Quinn***)
- **Renewal**
 - New submission deadline (from 6 to 9 months before expiry of the MA)
 - Updated content of the renewal application



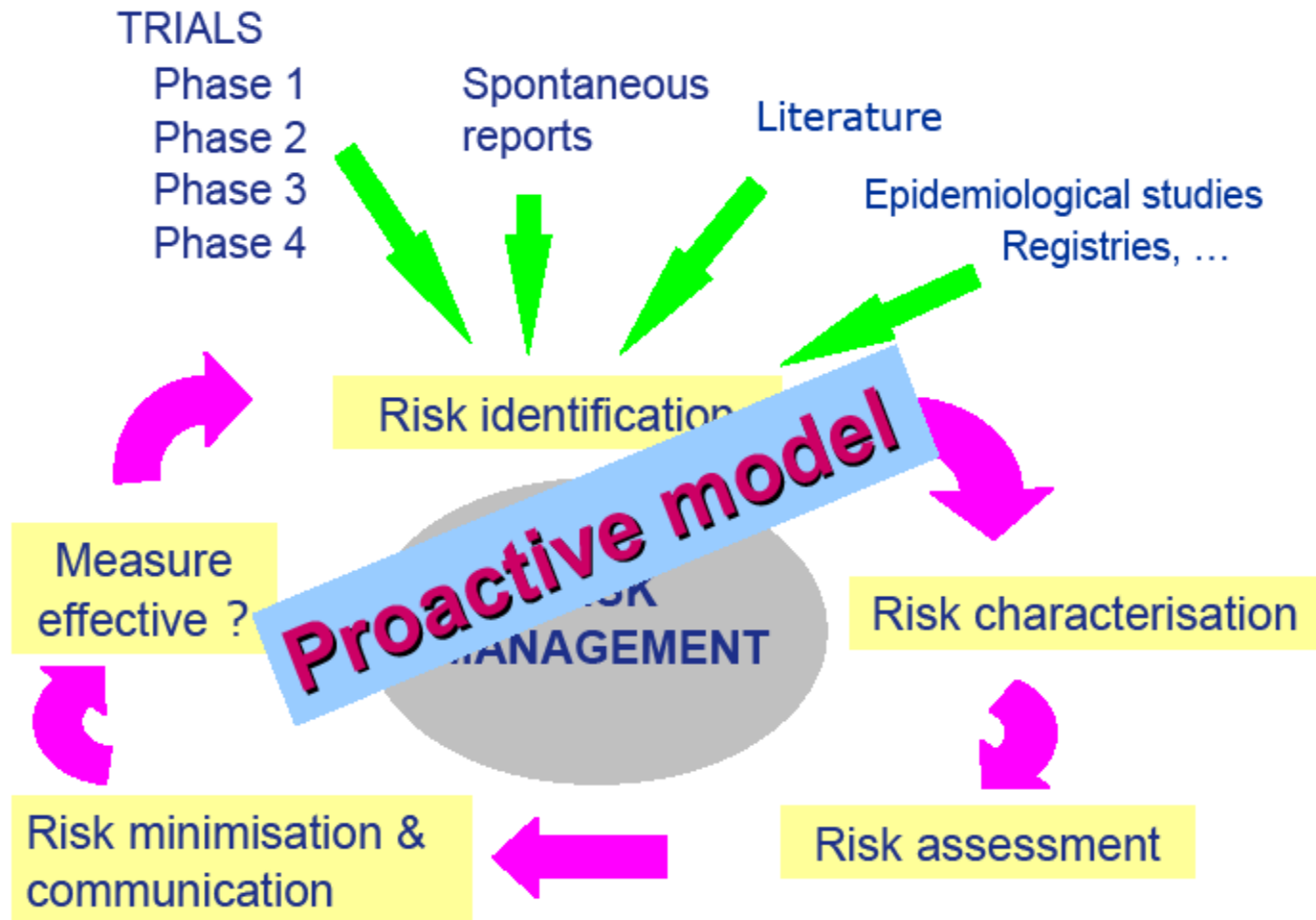
Proactive Pharmacovigilance

Risk Management Plans embedded in legislation.

- Will be required for all new applications.
- RMP should be proportionate to risks
- Obligation to monitor the effectiveness of Risk Minimisation
- Key role of PRAC in relation to RMP
- PASS may be condition of MA
- PAES may be condition of MA
- Summary of the RMP to be made public



Risk Management Plans



Benefit-risk evaluation: Changes to PSURs

1. **Scope:** Interval safety → Benefit-risk
2. **Format and content**
3. **Submission** (no *routine* submissions for generics, WEU, herbals, homeopathics)
4. **Frequency** (risk proportionate), as condition of the MA.
5. **Single EU assessment**
6. **Assessment deadlines** (defined in legislation).
7. **Outcomes** – legally binding
8. **Transparency**
(see afternoon presentation).



PSUR requirements – application of principle of risk proportionality

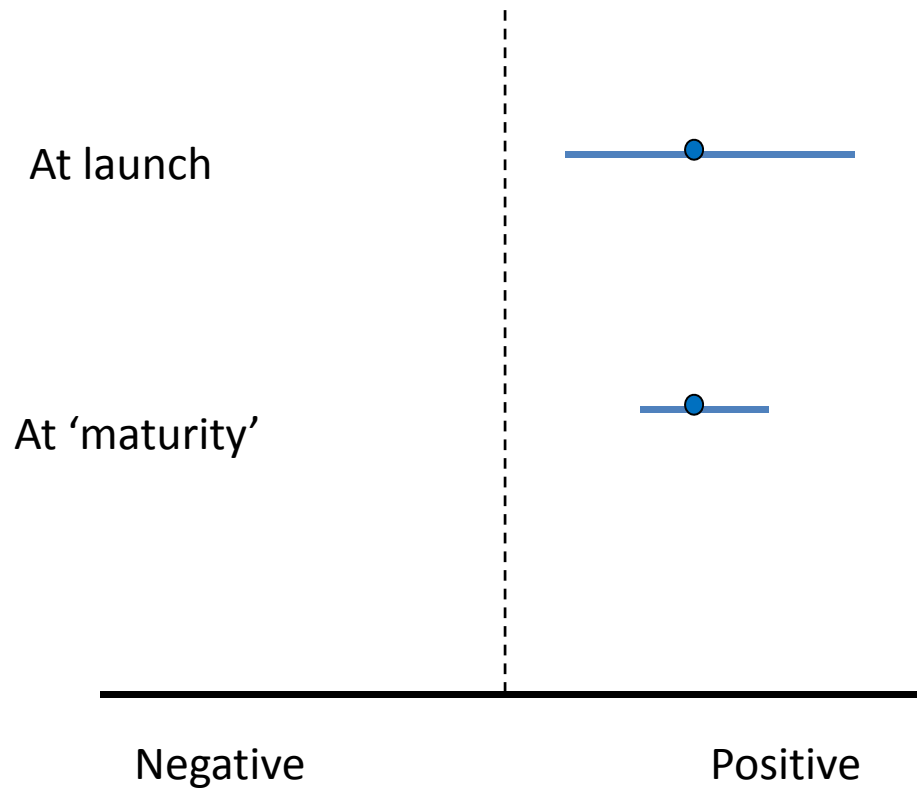
- No **routine** requirement for PSURs for **Generics** (Article 10(1) Dir. 2001/83/EC), **Well-established use** (Article 10a Dir. 2001/83/EC), **Homeopathic** (Article 14 Dir. 2001/83/EC) and **Traditional Herbal** (Article 16a Dir. 2001/83/EC) medicinal products.
- PSUR will be a B/R evaluation report based on cumulative data - ***line listings will no longer be routinely required***
- MAHs shall submit electronically to EMA - *after repository has been established*
- ***Single EU assessment – building on worksharing and removing duplication.***

(further detail in the afternoon presentation).





Estimated benefit risk



Estimated benefit risk



Changes to Data Collection Activities



Planned Changes for ICSRs

- Expansion of the definition of an ADR.
- Simplification of reporting requirements for MAHs
- ICSRs direct to Eudravigilance, reports from MAHs automatically forwarded to MS where ADR occurred
- Eudravigilance functionality to be met first
- Functional requirements to be drawn up by member states and European Agency
- Functionalities to be audited
- Article 107(3) applies 6 months after audit
- Current planning - EV ready for audit in 2015
- Ensuring clarity on transitional arrangements is a priority.



Signal Detection

- Legal requirement for data monitoring in EV.
- Common signal detection tools and outputs to be available to the Member States.
- Direct evidence that $> 54\%$ serious safety issues can be detected *earlier* if EV used *in addition to other resources*.

(Alvarez et al, 2010, Drug Safety 33(6) 475-487).





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EudraVigilance signal detection methods help detect drug safety issues earlier

Press release

EudraVigilance signal detection methods help detect drug safety issues earlier

Adding EudraVigilance statistical signal detection methods to routine drug safety monitoring methods leads to earlier detection of safety issues

An evaluation of the use of the European Medicines Agency's statistical signal detection method in the adverse drug reaction data collected in the EudraVigilance database has shown a significantly earlier detection of drug safety issues in about 54% of cases where a clinically important adverse drug reaction report was found (compared to 'routine' pharmacovigilance).

The study which was published in *Drug Safety*, the journal of the International Society of Pharmacovigilance, was carried out by the European Medicines Agency and was conducted in relation to centrally authorised medicines. It provides direct evidence for a strong additive role of EudraVigilance signal detection methods. The

Changes to Study Requirements



Post Authorisation Safety Studies

- A post-authorisation safety study is defined as “*any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures*”
(Article 1, Directive 2010/84/EU).



PASS

Implementing Measure

- Scope (of studies) – non interventional.
- Formats of study protocols, abstract and final study reports based on internationally agreed standards (*see presentation from Y. Buggy*).
- GVP – format recommended to be used for all non-interventional post-authorisation safety studies (including those initiated voluntarily by MAHs).





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Basis for PAES in the legislation - Directive 2010/84/EC

- “Such studies may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice.”
- “...to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed.”
- “to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised”



New procedures and decision making process

- **New decision making process (binding)**

For Union Procedures / PSUR / PASS

- CAP only -> CHMP / EC
- NAP only -> Coordination Group (by consensus) / EC (if no consensus)
- Mix CAP/NAP -> CHMP / EC

- **Involvement of PRAC**

- Union Procedures
- PSUR
- RMP
- PASS (condition to the MA) - for study to 'commence' after July 2012
(‘commence’ = start of data collection – *Implementing Measures*)

CAP: Centrally authorised products
NAP: Nationally authorised products



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SAFETY REFERRALS

TOMORROW'S TOOLKIT



The Future: 107(i) NAPs +(MRP/DCPs)+CAPs 1/2

Initiated by	→	MS/EC when urgent action is considered necessary + criteria
Time Limit	→	60 days (PRAC) 30 days (CHMP / CG)
Consultation	→	HCPs Public MAHs Written +/- public hearing



Quality system

- Legal management responsibility for **MAHs, competent authorities in MS and Agency.**
- Underpins all pharmacovigilance activities.
- Minimum requirements in Implementing Measure
- Requirements and guidance in GVP Module I
- Process-specific quality requirements and measures to monitor compliance and effectiveness in each GVP Module

(see presentation from S. Curran and M. Quinn)



Transparency and Public Participation



Product Information

Article 23, Directive 2010/84/EC

.....The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

(Union Procedures, PSURs, PASS)



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Public/Patient Participation and Transparency

- Direct patient reporting
- Additional monitoring – black symbol and advice in PLs
- Transparency of information via Web-portals
- Representation in Committees
- Public hearings in context of Union Procedures
- User testing
- Interaction PCWP-PRAC and HCPWG-PRAC, ad hoc consultation with patient and healthcare professional representatives


(see presentations from C.Fisher and F Houyez)





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National Monitoring Overview

This update provides an overview of the reports of suspected adverse reactions received by the IMB in association with **Gardasil**. It includes all reports received up to the end of June 2011 and incorporates the first year of the HSE human papillomavirus (HPV) Schools Immunisation Programme.

[Overview of National Monitoring Experience with Gardasil](#)

Transparency

Regulation EU 1235/2010 states that in order to increase transparency as regards as pharmacovigilance issues a European medicines web portal should be created and maintained by the Agency in collaboration with Members States and the Commission



Decisions

Assessments

**Opinions
Agreements
Positions**

Recommendations

Available
to the public



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24 November 2011
EMA/CHMP/PhVWP/909637/2011
Patient Health Protection

Monthly report

Issue number: 1111

Pharmacovigilance Working Party (PhVWP) November 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its November 2011 plenary meeting on 14-16 November 2011.

Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy. The positions agreed by the PhVWP for non-centrally authorised products

Information and Consultation

- European Commission's Implementing measures
- GVP Development on target – consultation on first wave modules to start by February 2012.
- Development of transitional guidance
 - A joint exercise between EC / EMA / MS
 - Implementing Measures
 - Legal and operational guidance on transitional measures - will be published on EC/EMA/HMA websites



Conclusions

- Far reaching changes based on wide recognition of need to safeguard public health via effective pharmacovigilance and risk management.
- Collaborative working, prioritisation and consultation are essential for successful implementation
- Opportunity to build on successful strategies and to generate momentum for partnerships and collaboration to better protect and promote public health.



Questions?



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