Agenzia Italiana del Farmaco

La Farmacovigilanza nell'Unione Europea

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Pharmacovigilance

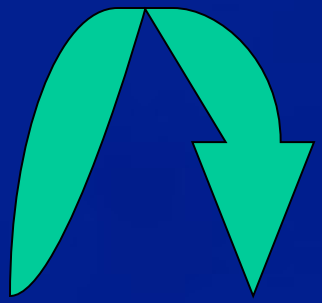
"The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems"

(WHO definition)

Directive of the European Parliament and Council amending Dir. 2001/83

- Aims – pharmacovigilance (PhV)
  - The criteria of **quality**, **safety** and **efficacy** should enable the benefit/risk balance of all medicinal products to be assessed both when they are placed on the market and at any time the competent authority deems this appropriate.
  - In the field of PhV account should be taken of the facilities offered by new information technologies to improve exchanges of knowledge among Member States (MS)

“Pharmacovigilance Planning”



The future has already started

Background

- Once a product is marketed, detailed evaluation of the information generated through pharmacovigilance activities is essential to ensure the safe use

- Industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities before a license is granted

Aims of Pharmacovigilance

- to improve patient care and safety
- to improve public health and safety
- to contribute to the assessment of benefit, harm, effectiveness and risk of medicines,
- to promote education and clinical training
- to promote effective communication to the public
- to promote rational and safe use of medicines

PHARMACOVIGILANCE AND REGULATORY ACTIVITY
Principles

- Planning of pharmacovigilance activities throughout the product life-cycle
- Science-based approach to risk documentation
- Effective collaboration between regulators and industry
- Applicability of the Pharmacovigilance plan across the three ICH regions (EU – USA - Japan)

Pharmacovigilance Planning…
Objectives

- Aid industry and regulators in planning pharmacovigilance activities (early postmarketing period of a new drug)
- Setup a method for documenting risks
- Provide a structure for a pharmacovigilance plan

MAIN TARGETS

- New chemical entities
- Biotechnology derived products
- New dosage forms
- New route of administrations
- New manufacturing process of a biotechnologically-derived product
- New populations
- Significant new indications

Pharmacovigilance and Regulatory Communication

- Pharmacovigilance Specification
- Pharmacovigilance Plan
- Pharmacovigilance Methods

Pharmacovigilance Specification

Summary of the identified risks of a drug, the potential for important unidentified risks, the populations potentially at-risk and situations that have not been adequately studied in RCTs

↓

to facilitate the construction of the Pharmacovigilance Plan

Pharmacovigilance and Regulatory Communication

Pharmacovigilance specification and Pharmacovigilance plan might be submitted at the time of licence application

Planning and dialogue with regulators should also start before licence application

Pharmacovigilance plan

It is a structure for documenting the proposed pharmacovigilance methods to address the issue identified in the pharmacovigilance specification

It can be a stand-alone document but elements could also be incorporated into the Common Technical Document for a new or modified product

Pharmacovigilance plan

- The plan would normally be developed by the sponsor and can be discussed with regulators:
  - during product development
  - prior to approval of a new product
  - when safety concern arises post-marketing

Pharmacovigilance and Regulatory Activity
ROUTINE PHARMACOVIGILANCE PRACTICE

- should be conducted for all medicinal products
- includes systems and processes that ensure the quality of pharmacovigilance and the report for regulatory authorities
- includes continuous monitoring of the safety profile
- includes local regulatory requirement to present an overview of the company's organization and practices for conducting pharmacovigilance

PHARMACOVIGILANCE PLANNING

DIVERSITY ACROSS EUROPE

RESOURCE

SYSTEMS

EXPERTISE

IT WILL BE IMPORTANT TO HAVE A COMPREHENSIVE PICTURE OF THESE ASSETS

COHERENT EUROPEAN RISK MANAGEMENT STRATEGY

The need for core performance standards

↓

An effective issues tracking and management system

↓

Agreed methodologies for audit and monitoring outcomes

Pharmacovigilance and Regulatory Activity
Competent Authorities

EACH NATIONAL COMPETENT AUTHORITY PLAYS THE CRUCIAL ROLE TO THE EFFECTIVENESS OF PHARMACOVIGILANCE EUROPEAN SYSTEM

(Notice to Applicants Volume IX)

PHARMACOVIGILANCE AND REGULATORY ACTIVITY

"Best Evidence" is fundamental to strengthen pharmacovigilance

Better Utilisation of Databases for epidemiological studies

Systematic collection of Drug Utilisation Data

THE TASK FOR REGULATORY AGENCIES IS TO ACHIEVE HIGH STANDARDS OF PUBLIC HEALTH PROTECTION FOR ALL MEDICINES

ICH E2E Step 2 Guideline
Purpose

- First high level ICH guideline
- Encourage harmonization and consistency
- Prevent duplication of effort
- Benefit to public health programs throughout the world as they consider new drugs in their countries
- The guideline does not describe other methods to reduce risks from drugs, such as risk communication

NEW ICH PHARMACOVIGILANCE TOPICS

- **E2C (S) - Addendum to ICH E2C**
  "Clinical Safety Data Management - Periodic Safety Update Reports for Marketed Drugs" - step 4
  Feb 2003 (V1)

- **E2D - Post Approval Safety Management:**
  Definitions and Standards for Expedited Reporting and Good Case Management Practices - ? Step 2
  July 2003 (V2)

- **E2E - Pharmacovigilance Planning (PhVP) - ? Step2**
  November 2003 (V3)

ICH Pharmacovigilance Planning

Scope of guideline:

- Help industry prepare a pharmacovigilance plan for discussions with regulators during the licensing assessment and prior to product launch.
- New chemicals/biologicals, new formulations, populations and indications.

3 components:

- Pharmacovigilance 'specification'
- Pharmacovigilance plan
- Post-approval safety studies (design and conduct)
- NOT risk reduction tools

ICH Pharmacovigilance Planning

Note: not risk reduction tools (as dependent on delivery of healthcare)

ICH Pharmacovigilance Planning

Pharmacovigilance specification:

Structured method for documenting established risks, unidentified risks, at-risk populations and situations not studied.

Specification:

- pre-clinical: identified safety concerns
- pre-clinical: missing information
- clinical: size of the human safety database and frequency of ADRs that could have been detected in these trials
- clinical: other limitations of the database (Japan)
- clinical: adverse drug reactions (based on CCDS)
- clinical: adverse reactions that require further evaluation
- clinical: safety signals requiring evaluation
- clinical: populations not studied in the pre-approval phase
- clinical: documented interactions
- clinical: the potential for unidentified interactions
- disease and AE epidemiology + class ADRs.

ICH Pharmacovigilance Plan

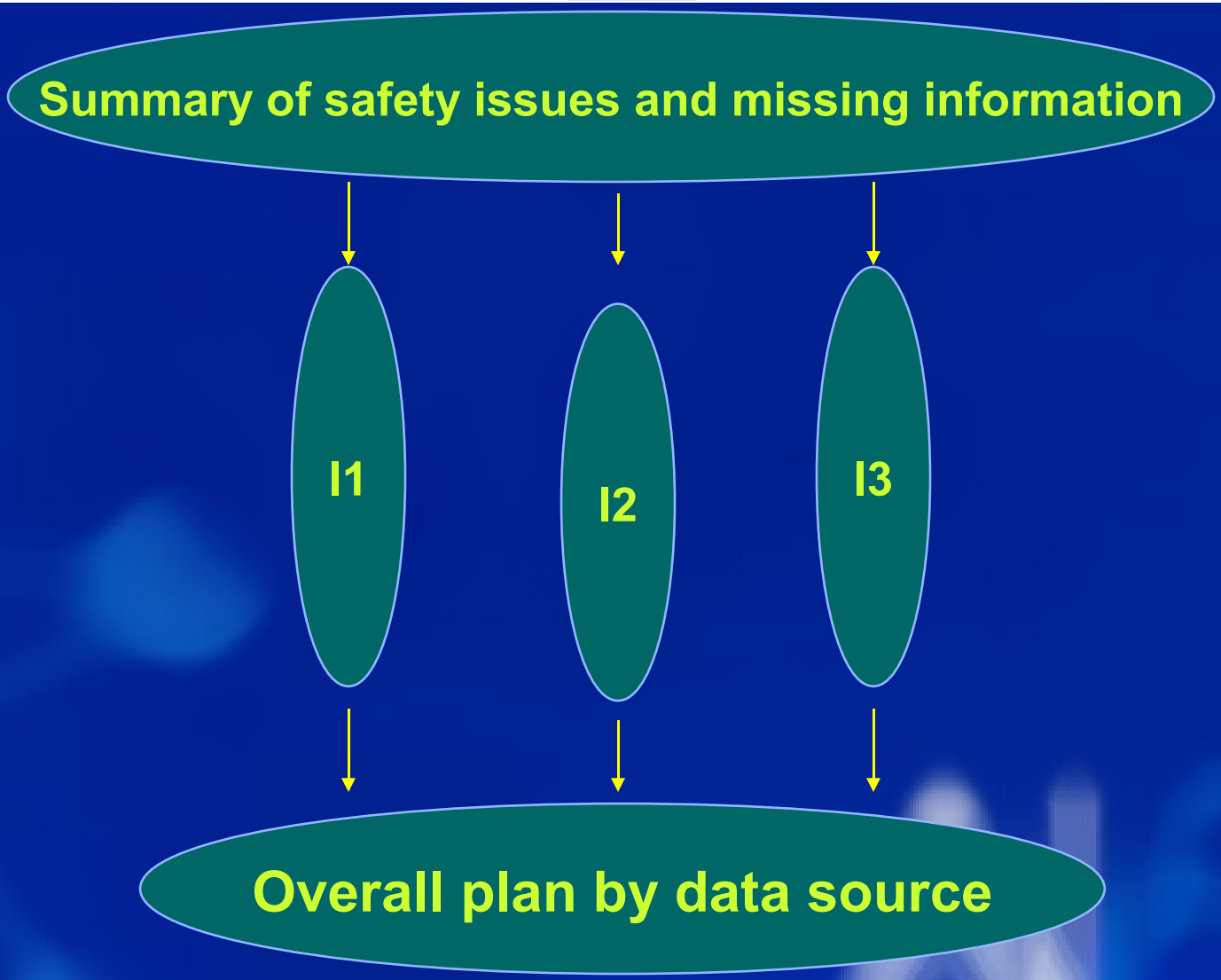
Pharmacovigilance plan:

- Based on the specification
- Proposes the data collection required post-approval
- Collection of information ‘missing’ pre-approval
- Post-approval milestones
- May outline protocol for clinical safety study etc.
- Used as discussion document pre-approval between industry and regulators
- Update the plan as data become available

Pharmacovigilance Plan

Pharmacovigilance Plan: framework

- ✓ list risk issues and missing information
- ✓ company routine PhV practice (all products) - organisation, training, case reporting, PSURs, signal detection, evaluation, labelling, issue management, Info management, QA, etc.
- ✓ safety action plan for specific issues / missing information: basis, objective of action, action proposed, company lead, timing of evaluation / reporting.
- ✓ Overall action plan by data source


Summary of safety issues and missing information
I1
I2
I3
Overall plan by data source

ICH Pharmacovigilance Planning

Post-approval safety studies. The guideline will set out:

- "best practice for the design and conduct of post-approval clinical safety studies"
- major debate on what should be included

Design

- Advice on protocol elements
- Describe individual data collection methodologies + strengths and weaknesses ????
- Suggest possible data collection options to address specific issues e.g. interactions, elderly, long-term safety, pre-clinical concerns ????
- Advice on ethics ????

ICH Pharmacovigilance Planning

- Post-approval safety studies - conduct:
  - As Volume IX of Notice to MAH ???? - risk in EU
  - Existing ISPE guidelines
  - Interaction with regulators / reporting
- Annex:
  - terms and definitions
  - details on study designs

ICH Pharmacovigilance Planning

Conclusion:

- Important CHMP and its working parties input into the ICH process
- Need to agree how best to get EU input
- Need to consider how to pilot use of plans in Europe

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PMS studies

Early Post Marketing Surveillance Studies

APPROVAL UNDER EXCEPTIONAL CIRCUMSTANCES
Art. 13(2) Council Regulation 2309/93

- Limited clinical data available because:
  - **rare disease ("orphan disease")**
  - **current scientific knowledge does not allow a comprehensive assessment**
  - **ethical constraints in performing conventional RCTs**
- "Specific Obligations" (i.e. PASStudies) should be carried out within an agreed timeframe
- Annual re-assessment of the benefit/risk ratio by the CHMP
- The SPC should contain this information

Early Post Marketing Surveillance Studies

- There are at least two situation where intensified early post-marketing surveillance in necessary:
  - Clinical studies have shown the potential for a MP to be associated with severe ADRs, but this risk has not been properly quantified or has been measured in selected patient population only.
  - Clinical studies have not shown any serious safety concerns for a drug, but its pharmacological properties, the toxicological data or the data from drugs of the same class give suspicion for a high potential for developing severe ADRs.

in progress ICH E2E
Pharmacovigilance Planning

- Scope of guideline:
  - to help industry prepare a PhV plan for discussions with regulators during the licensing assessment and prior to product launch.
- The components
  - **Pharmacovigilance "specification";**
  - **Pharmacovigilance plan;**
  - **Post approval safety studies - PASS.**

in progress ICH E2E
Pharmacovigilance Planning

- Background
  - The decision to approve a drug is based on it having a satisfactory balance of benefits and risks within the conditions specified in the product labelling. This decision is based on the information available at the time of approval. The safety profile of the MP may change over time through expanding its use in terms of patient target and the number of patient exposed. In addition, during the early post marketing period, the new drug use will be expanded to setting different from RCTs.

in progress ICH E2E
Pharmacovigilance Planning

- Background
  - Once a MP is marketed, much new information will be generated, which may impact on the benefits/risks of the MP, and evaluation of this information needs to be an on-going process, by both MAHs and regulatory authorities. Detailed evaluation of the information generated through PhV activities is a vital process to ensure safer use of the MP concerned. The benefit/risk balance can be improved by reducing risks to patients through effective PhV and risk management through information feed-back in a timely manner.

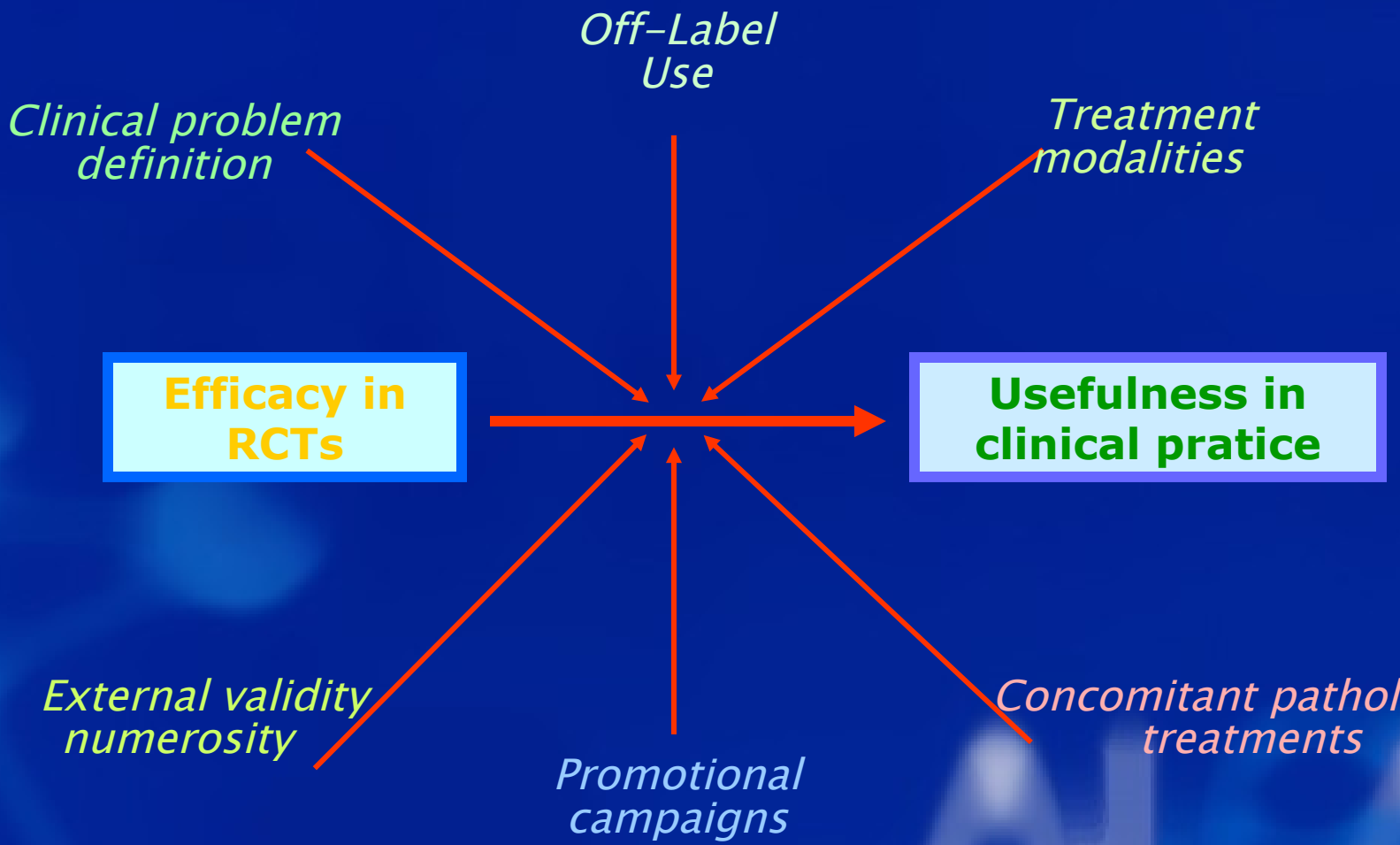
in progress ICH E2E
Pharmacovigilance Planning

- Industry and regulators have identified the need for better and earlier planning of PhV activities before a licence is granted; this need is based on:
  - **the increasingly innovative technologies being employed in drug development;**
  - **approval of medicines on limited pre-approval dossiers;**
  - **the globalisation of the pharmaceutical industry;**
  - **high profile drug withdrawals due to safety concerns.**

WHO: essential drugs and medicine policy

- The impact of regulation on safe use of drugs - EDM/QSM/2002
  - There had been major advances in the area of PhV and drug safety, but:
    - **many gaps remained, particularly in the area of communicating safety information;**
    - **a need is identified for the presence of feed-back mechanisms to guide authorities as to whether their interventions created a significant public health impact;**
    - **the greater transparency and a judicious communication of information to the media was in order.**

Observational Epidemiological Studies



Observational Epidemiological Studies

- Useful to generate evidence on post-marketing safety
- Needed to resolve in a sufficiently quick way for possible safety problems (a prospectic trial would require an unacceptably long period of time)
- Should rely on high quality data in population databases capable to register both exposure to drugs and individual medical events. Flexibility in order to allow adjustments for confounding factors.

Observational studies and prescription habits: OBJECTIVES

- To improve the knowledge of the characteristics of the treated population
- To assess the APPROPRIATENESS of drug use
- To improve the assessment of TOLERABILITY profile
- To identify predictive variables for the optimisation of the EFFICACY profile
- To educate prescribers to cautiously use new drugs

Public Health Decisions based upon the best possible knowledge related to the ACTUALLY TREATED population

Post Marketing safety studies

- Importance of confirmatory epidemiological studies;
- Importance of public conduction of those studies
- Importance of performing those studies in the early post-marketing phases;
- Importance of identifying excellence centres at European level;
- Importance of networking those centres.

Public health protection

Post-Marketing Surveillance Studies

- Useful to generate evidence on post-marketing safety
- Needed to resolve in a sufficiently quick way for possible safety problems (a prospectic trial would require an unacceptably long period of time)
- Should rely on high quality data in population databases capable to register both exposure to drugs and individual medical events. Flexibility in order to allow adjustments for confounding factors.

In case of future need of PMS in the same fields

- Network of excellence centres
- Established activities in Regional and Local administration
- Collaboration between excellence centres and GPs
- Availability of large data bases

What's an excellence centre

- Trained Health Care Professionals
- Expertise in the diagnostic process
- Part of a network
- Guarantee of adherence to the protocol and rapid implementation if needed
- Harmonised approach
- Capability to recruit an adequate n° of patients
- Audit on outcome
- Clear communication with GPs
- Optimised accessibility to the treatments for all patients

LA GESTIONE DEL RISCHIO CARDIOVASCOLARE

Priorità di salute pubblica per il 2004

Progetto RiACE

Rischio **A**ssoluto **C**ardiovascolare **E**pidemiologia

La ricerca di esito come parte integrante dell'atto regolatorio

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Benefit / risk balance

RISK MANAGEMENT

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

Note for guidance on procedure for competent authorities on the undertaking of PhV activities - CHMP/PhVVP/175/95 Rev.1

- Management of PhV data
  - Spontaneous reporting system
  - MAH derived PhV data
  - PhV data from other sources
  - Procedures for communication and evaluation of PhV issues within the EU

Informazioni di farmacovigilanza: pre e post AIC

- *Dati accessibili: RCT*
  - *epidemiologia della malattia*
  - *profilo pre-clinico di safety*
  - *ADRs emerse nei RCT ad un dato livello di potenza statistica*
  - *interazioni documentate*
  - *effetti di classe*
- **Dati non accessibili: post-marketing**
  - **missing pre-clinical data**
  - **teratogenicità / mutagenicità**
  - **ADRs non definite e interazioni**

Safety Signals

- An apparent excess of adverse events associated with a product's use
  - a single well-documented case report may be viewed as a signal
  - preclinical findings
  - experience with other similar products in the class
- May be further assessed in terms of magnitude, population at risk, changes in risk over time, biological plausibility and other factors.

Safety Signals May Be...

- New unlabeled adverse events
- An observed increase in the severity or specificity of a labeled event
- An observed increase in the frequency of a labeled event
- New interactions
- Confusion with a product's name, packaging or use, either actual or potential

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

Understanding Safety Signals

- Demographics - age, gender, race
- Effect of exposure duration and dose
- Relationship between concomitant medications and potential interactions and the risk of event
- Relationship between co-morbid conditions and the risk of event

Understanding Safety Signals (cont'd)

- Effects of lot-to-lot variation and differences in product formulation and the risk of the event
- Potential for an excess of adverse events given the disease being treated
- Estimates of the magnitude of risk or differences from known background rates

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

Beneficio/rischio:
3 livelli di valutazione

- AUTORITA' REGOLATORIE
  - valutare i benefici/rischi per la popolazione;
- MEDICI
  - valutare i benefici/rischi per uno specifico paziente;
- PAZIENTE
  - valutare i benefici/rischi in termini di valori personali.

Evaluation of causality

- Individual level
- Case Collection
- Importance of Case definition (confirmation of diagnosis): CIOMS , MSSO
- Importance of quality
- Necessity: reported adverse event maybe related to concomitant medication or coexisting disease

Individual adverse event causality assessment -Pros

- Better case quality and follow up
- Surfaces confounding factors and follow- up needs while case is fresh
- Allows ongoing signal assessment by number of reports considered probably, possibly or unlikely to be related

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

CHMP PhV Working Party

- Risks reduction strategies
  - The benefit/risk has been previously evaluated during the pre-marketing phase. The risk estimation is based on all available scientific data, but also takes into account risk reduction strategies including:
    - **Information in the SPCs**
    - **Systematic post-marketing surveillance.**

VALUTAZIONE DELLA POSSIBILITÀ DI CONTROLLARE IL RISCHIO

RIVALUTAZIONE DEL RAPPORTO RISCHIO/BENEFICIO (ANCHE IN CONSIDERAZIONE DI POSSIBILI ALTERNATIVE TERAPEUTICHE)

FAVOREVOLE

- DEAR DOCTOR LETTER
- MODIFICA POSOLOGIA E/O INDICAZIONI CONTROINDICAZIONI
- AVVERTENZE SPECIALI
- STRETTO MONITORAGGIO

SFAVOREVOLE

- RITIRO

Types of Public Health Programmes

- Education
- Lifestyle and behavioral changes
- Environmental modifications
- Nutritional interventions
- Drug administration programmes
  - Mass control programmes
  - Case specific programmes
  - Individual treatment programmes

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

Note for guidance on procedure for competent authorities on the undertaking of PhV activities - CHMP/PhVVP/175/95 Rev.1

- The National PhV Centre maintain regular contacts with the healthcare professionals by:
  - **the publishing of regular ADRs bulletins**
  - **the sending of "Dear Doctor Letters", where appropriate**
  - **the provision of requested information on one-to-one basis where possible**

La nuova strategia di comunicazione-informazione

- A chi rivolgersi
- Cosa comunicare
- Come diffondere l'informazione
- Scopo della comunicazione in farmacovigilanza

Principi fondamentali della comunicazione

- Deve rispondere alle necessità della comunità – paziente
- Deve essere bilanciata in relazione al R/B
- Tutti gli aspetti, le evidenze necessarie alla valutazione – comprensione del rischio e del beneficio devono essere chiaramente descritti
- Deve differenziarsi in diversi livelli per rispondere alle diverse necessità dei riceventi: specificatamente indirizzata

Erice Declaration 1998
on communicating information drug safety

- Incoraggiare i più alti livelli etici, professionali e scientifici nell'attività di protezione e promozione dell'uso corretto dei medicinali
- Implementare politiche di intervento riguardo: beneficio – danno – efficienza – rischio e la loro comunicazione ai pazienti trasparente e completa
- Sottolinea la necessità di onestà e responsabilità nella comunicazione sulla sicurezza dei medicinali
- Auspica che i pazienti debbano essere apertamente informati sulle evidenze, le conoscenze e le incertezze riguardo il profilo di sicurezza dei medicinali

Strumenti per la corretta comunicazione

- Educazione alla valutazione del beneficio/rischio e diffusione della informazione
- Ottimizzazione della prescrizione dei medicinali, monitoraggio della sicurezza
- Sistema di guida per la corretta prescrizione (Note CUF - EBM - Cochrane)
- Misure di out-come per valutare l'efficacia della comunucazione

Finalità della corretta comunicazione

- Aumentare la trasparenza
- Esplicitare la motivazione della decisione, riportandone la complessità
- L'impatto di tutte le ipotesi possono essere valutate
- Motivare chiaramente la decisione intrapresa
- Valutare le misure di out-come per verificare l'efficacia della comunicazione ed il livello di comprensione

Risk Analysis

- Identification
- Quantification (Estimation)
- Evaluation

Risk Management

- Administrative measures (risk minimization)
- Risk communication
- Prevention strategies

Data

Decisions

Actions

Prevention strategies

- valutare l'efficacia della comunicazione relativa ai profili di rischio dei farmaci agli operatori sanitari e ai pazienti
- valutare il livello di compliance e di rispetto delle raccomandazione dei prescrittori, farmacisti e pazienti
- valutare l'impatto delle decisioni regolatorie sui livelli di mortalità/morbidità e di uso appropriato dei medicinali
- identificare precocemente le carenze delle implementazioni effettuate al fine di intrapprendere le azioni necessarie
- apprendere il corretto procedimento di gestione dei rischi legati all'utilizzo dei farmaci

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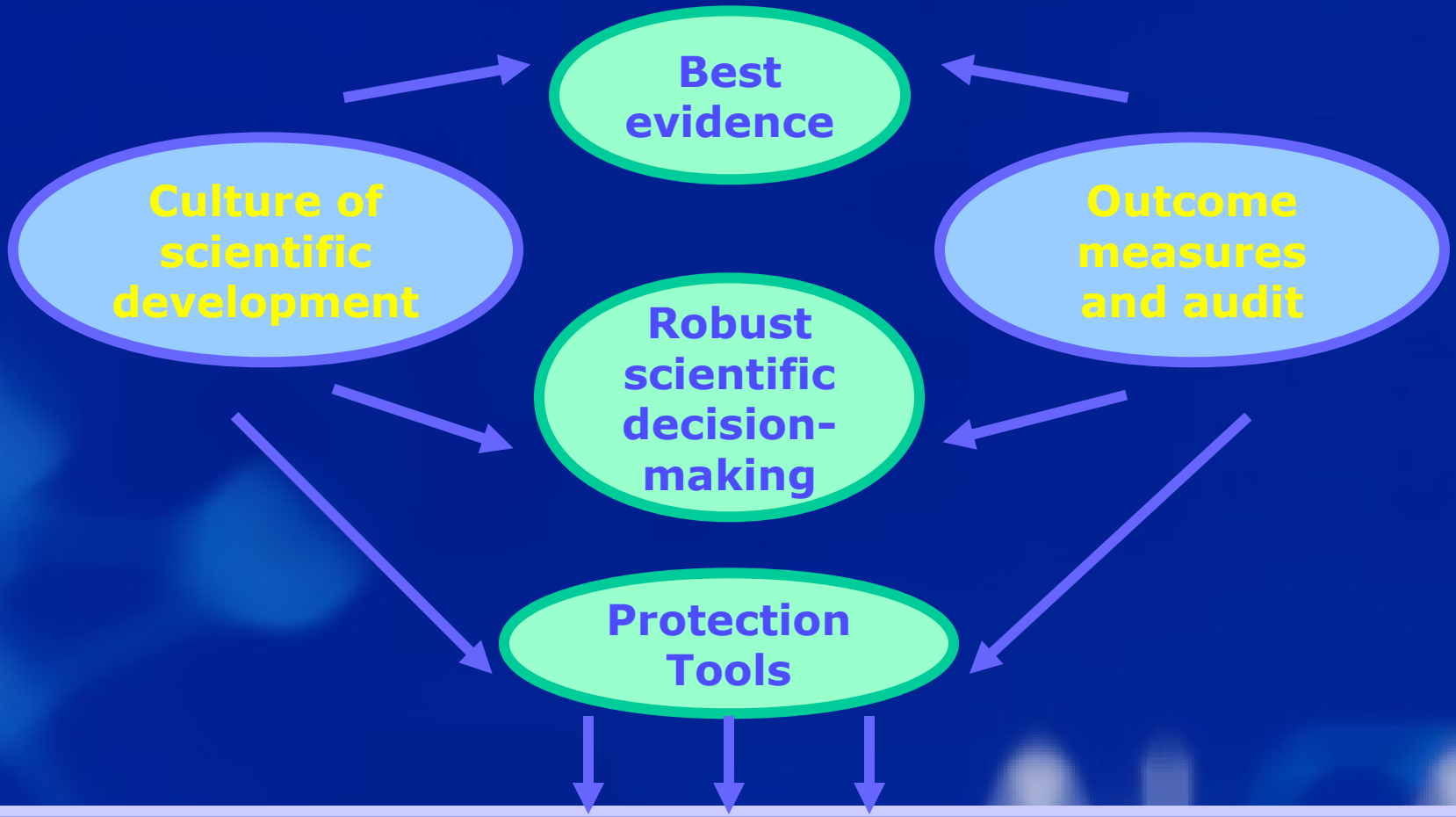

Measurable excellence in terms of Public Health Benefit

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Pharmacovigilance Working Party

Rapid Alert System

Non Urgent Information

Periodic Safety Updated Report

EMEA
EUROPEAN MEDICINES EVALUATION AGENCY

- Istituita con il Regolamento 2309/93 (art.49/63), l'Agenzia è responsabile del coordinamento delle risorse scientifiche messe a sua disposizione dalle Autorità competenti degli Stati Membri per la valutazione e la vigilanza dei medicinali

CHMP
Committee for Medicines for Human use

- Organo Tecnico Scientifico è composto da un rappresentante nominato da ciascuno Stato Membro, ed è responsabile di formulare opinioni scientifiche per conto dell'EMEA, sulla qualità, la sicurezza e l'efficacia dei prodotti medicinali.

PhVWP
Pharmacovigilance Working Party

- Sviluppo di di principi e procedure comuni per:
  - Generazione e valutazione dei segnali
  - Valutazione continua della sicurezza dei farmaci (PSUR)
- Sviluppo di principi e procedure comuni per lo scambio di informazioni e la comunicazione su:
  - problemi urgenti (rapid alert)
  - informazioni su richiesta
  - preparazione di linee guida
  - Sviluppo di metodi di farmacovigilanza in collaborazione con i programmi di ricerca in farmacovigilanza in Europa

Procedure di autorizzazione

CENTRALIZZATA	MUTUO RICONOSCIMENTO	NAZIONALE
•Unica domanda di autorizzazione per tutti i Paesi della CEE •Autorizzazione rilasciata dalla Commissione Europea •Vincomlante per tutti i Paesi della CEE •RCP-FI-Etichette identici in tutti i Paesi della Comunità	•Riguarda due o più Stati Membri •La prima autorizzazione è rilasciata dal RMS •Le autorizzazioni successive sono rilasciate dagli Stati Membri che riconoscono la prima autorizzazione •Può essere avviata sia su iniziativa dell'Azienda che di uno Stato Membro •RCP armonizzato	Rilasciata dai singoli Stati Membri

EUROPEAN PHARMACOVIGILANCE GUIDELINES
Attribuzione della responsabilità delle attività di farmacovigilanza

Prodotto a registrazione nazionale

Autorità nazionale dei singoli stati membri

Prodotti di Mutuo Riconoscimento

Autorità Sanitaria dei singoli Stati membri, le cui attività vengono normalmente coordinate dal Reference Member State

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Prodotti a registrazione centralizzata

Autorità sanitaria dei singoli Stati membri, sotto la guida ed il coordinamento del *Rapporteur* che ha anche il compito di produrre *Assesment Reports* ***in materia di*** *farmacovigilanza*

VOLUME 9-FARMACOVIGILANZA

- Le linee direttrici per la raccolta, la verifica, le modalità di presentazione dei dati; le funzioni le attività e le procedure di farmacovigilanza per l' industria e per le autorità regolatorie sono state raccolte in una linea guida nel volume 9 della Disciplina relativa ai medicinali nell'Unione Europea

Gestione delle segnalazioni

Tutti gli Stati Membri devono:

- Adottare provvedimenti atti ad incoraggiare le segnalazioni di presunti effetti indesiderati
- Istituire un sistema di Farmacovigilanza per raccogliere e valutare scientificamente le informazioni utili per la sorveglianza dei medicinali
- Trasferire le informazioni relative alle presunte reazioni avverse a medicinali agli altri Stati Membri ed all'Agenzia Europea per la Valutazione dei Medicinali (EMEA)

Per agevolare tale scambio di informazioni l'EMEA ha istituito Eudravigilance una rete informatizzata europea per il trattamento dei dati e la gestione di un data base centralizzato dalle segnalazioni di reazioni avverse ai medicinali autorizzati nell'UE

EUDRAVIGILANCE REQUISITI TECNICI

- Modalità, formati e terminologia sono standardizzati e contenuti in linee guida elaborate dalla Conferenza Internazionale per l'Armonizzazione ICH

- ICH M2: Gateway Recomendation for electronic transfer of Regulatory Information (ESTRI-GATEWAY)
- ICH E2BM: Message and Individual Case Safety Report Specifications
- ICH M1: Medical Dictionary for Regulatories Activities (MedDRA)
- ICH E2A Definitions and Standards for Expedited Reporting

MedDRA

- Dizionario medico per le attività di regolamentazione è costituito dalla terminologia medica internazionale, elaborata nell'ambito della Conferenza Internazionale dell'Armonizzazione dei requisiti tecnici per la registrazione dei prodotti farmaceutici.

MedDRA include:

- segni
- sintomi
- patologie
- diagnosi
- indicazioni terapeutiche
- nomi e risultati qualitativi compresa la
- farmacocinetica
- procedure mediche e chirurgiche
- storia familiare/sociale/medica

- Uso della terminologia per inserimento, recupero, valutazione e presentazione dei dati in:

- studi clinici
- segnalazioni spontanee
- documenti ufficiali presentati alle autorità
- informazioni regolamentate sul prodotto

I termini in MedDRA sono organizzati in base a tre categorie di rapporti:

- **equivalenza**: raggruppa termini sinonimi o equivalenti nei PT
- **gerarchico**: fornisce gradi o livelli di sovraordinazione e subordinazione che rappresentano i collegamenti verticali della struttura
- **associativo**: collegamenti orizzontali di termini che non sono né equivalenti né gerarchicamente collegati

PSUR
Periodic Safety Update Report

- E' La raccolta di tutte le informazioni relative alla sicurezza "globale" del farmaco dal momento della sua autorizzazione, accompagnata da una valutazione critica del rapporto beneficio/rischio: è un obbligo per il titolare dell'AIC anche per prodotti non commercializzati

PSUR - Contenuto

- Situazione registrativa globale
- Indicazioni cliniche
- Rifiuti dell'autorizzazione ricevuti
- Misure relative alla sicurezza intervenute successivamente all'autorizzazione
- Stima della popolazione di pazienti esposti al farmaco (dati di vendita)
- Elenco delle segnalazioni spontanee
- Segnalazioni provenienti da studi clinici
- Segnalazioni da letteratura
- Company Core Safety Information – Documento di base sulla sicurezza fornito dall'azienda

Agenzia Italiana del Farmaco

Procedure per la raccolta e o scambio di informazioni

- R.A.S. Rapid Alert System
  - Problemi urgenti relativi alla efficacia ed alla sicurezza
- N.U.I.S. Non Urgent Information System
  - Problemi non urgenti relativi alla efficacia ed alla sicurezza

Rapid Alert System

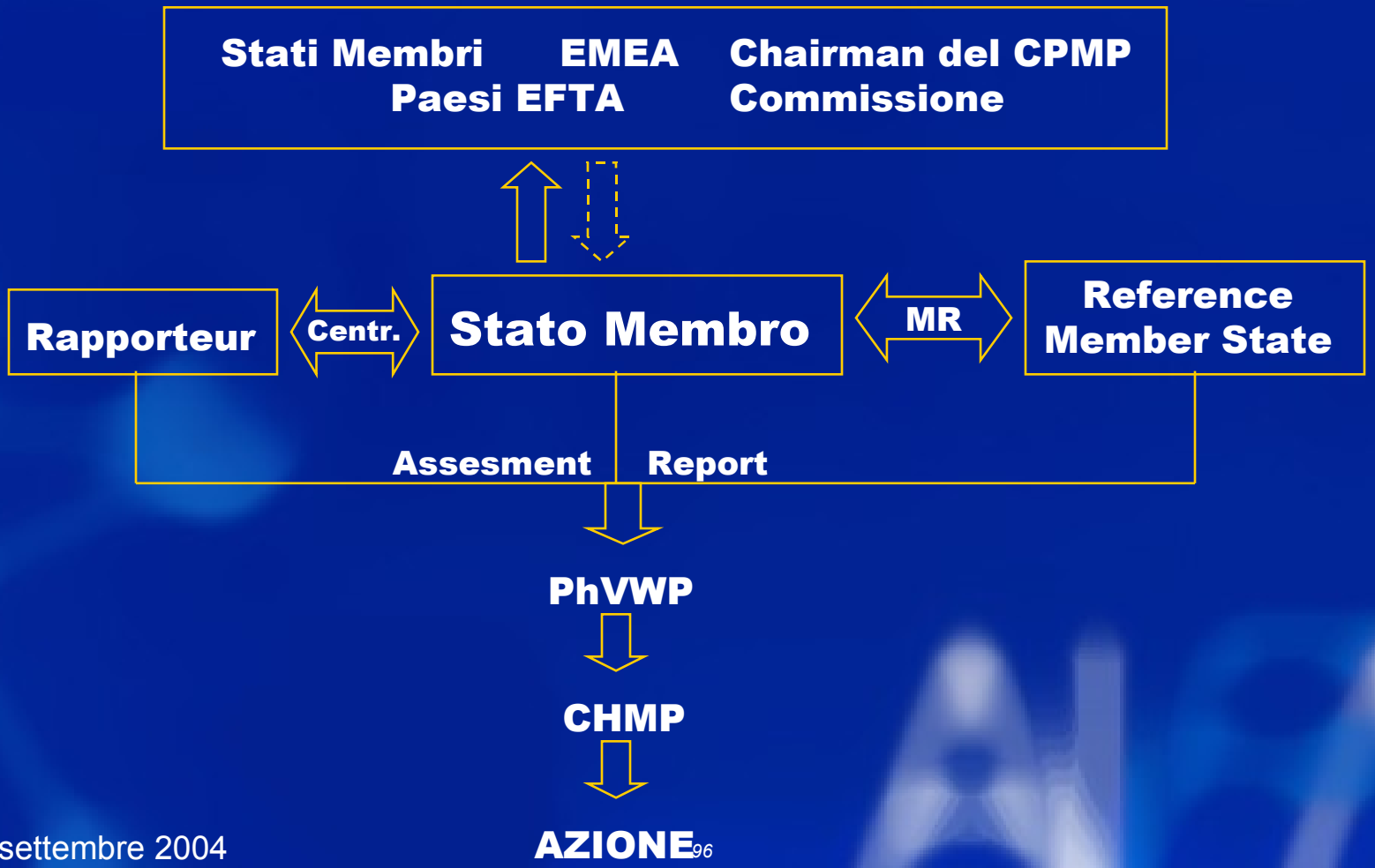
Misure urgenti per la salvaguardia della salute pubblica, derivanti da un cambiamento del rapporto beneficio/rischio

- Sospensione o revoca dell'autorizzazione
- Richiamo del prodotto
- Modifiche dell'R.C.P relative alla sicurezza o a restrizioni di indicazioni

Rapid Alert System

- Aumento del numero di segnalazioni
- Reazioni attese ma di maggior gravità che identificano nuovi fattori di rischio
- Aumento di frequenza di reazioni gravi
- Risultati di studi clinici
- Acquisizioni che mettono in discussione l'efficacia (peggioramento del rapporto beneficio/rischio)

Rapid Alert System



REFERRAL

- E ‘ una procedura che consente allo Stato, alla Ditta, alla Commissione Europea, di chiedere il parere del CHMP ogni volta che sorge una questione di qualità, sicurezza ed efficacia che coinvolge un interesse comunitario e per il quale le parti coinvolte non giungono ad un accordo.
- Si conclude con una decisione finale vincolante per tutti i contendenti ed in tutta la UE