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GaBI Scientific Meetings

ROUNDTABLE ON BIOSIMILARS
Pharmacovigilance, Traceability, Immunogenicity

15 November 2016, Real Academia Nacional de Farmacia, Madrid, Spain

Understanding pharmacovigilance for biologicals and the current challenges in Spain

Professor Francisco José de Abajo, MD, MPH, PhD, Spain

15 November 2016

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

Universidad de Alcalá

PPCI
Pro Pharma Communications International

Understanding pharmacovigilance for biologicals and the current challenges in Spain

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ROUNDTABLE ON BIOSIMILARS SPAIN
Pharmacovigilance, Traceability, Immunogenicity

Contents

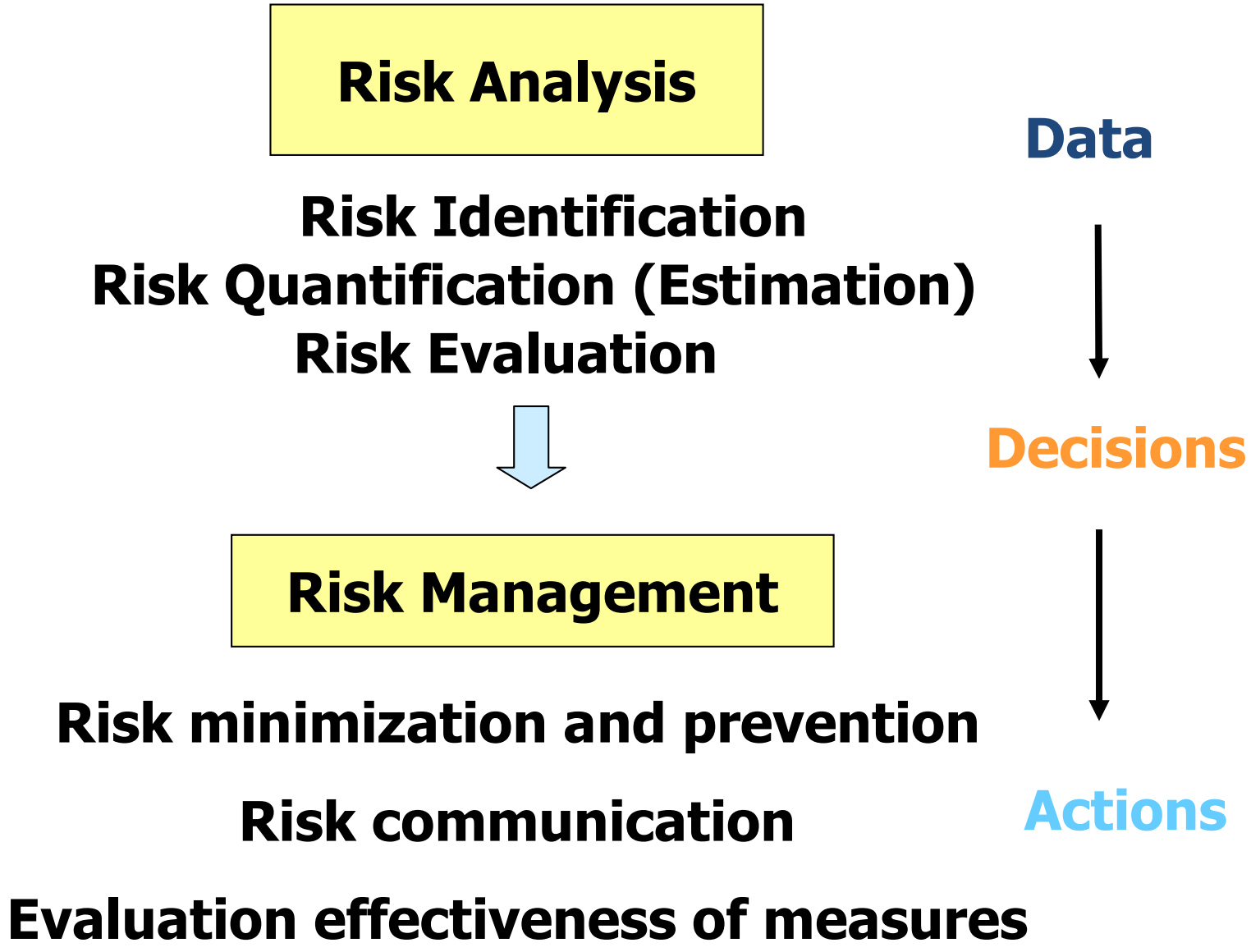
- Pharmacovigilance
  - Concept, operational framework
  - Reactive vs. Proactive pharmacovigilance
  - Risk Management Plan
- What is different with biologicals?
  - Immunogenicity
  - The importance of changing the manufacturing process
    - The case of Eprex (Epoetin alfa)
  - Implications for biosimilars
- Challenges and opportunities in Spain
  - Reporting ADRs from biologicals
    - The Spanish Pharmacovigilance System
    - Particular issues for biologicals: traceability
  - Specific strategies in pharmacovigilance of biologicals
    - Limitations of automated databases
      - Hospital-based treatments
    - Registries of persons exposed: BIOBADASER, BIOBADADERM
      - Signal generation, signal evaluation and effectiveness of minimization measures

Pharmacovigilance

- “A public health activity aimed at the identification, quantification, evaluation and prevention of the risks associated with the use of these medicinal products once they are marketed”

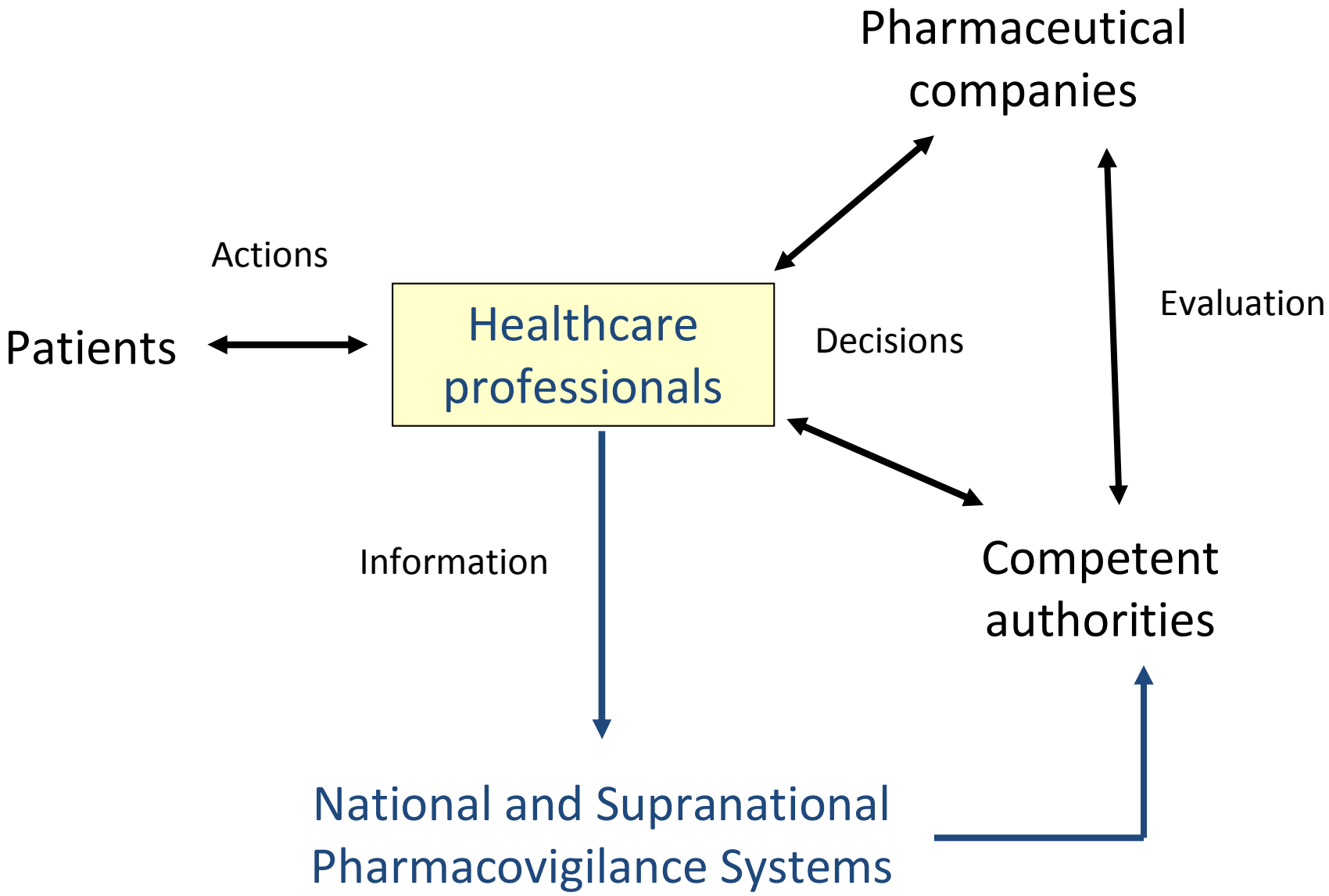
Royal Decree 577/2013

Pharmacovigilance operational framework



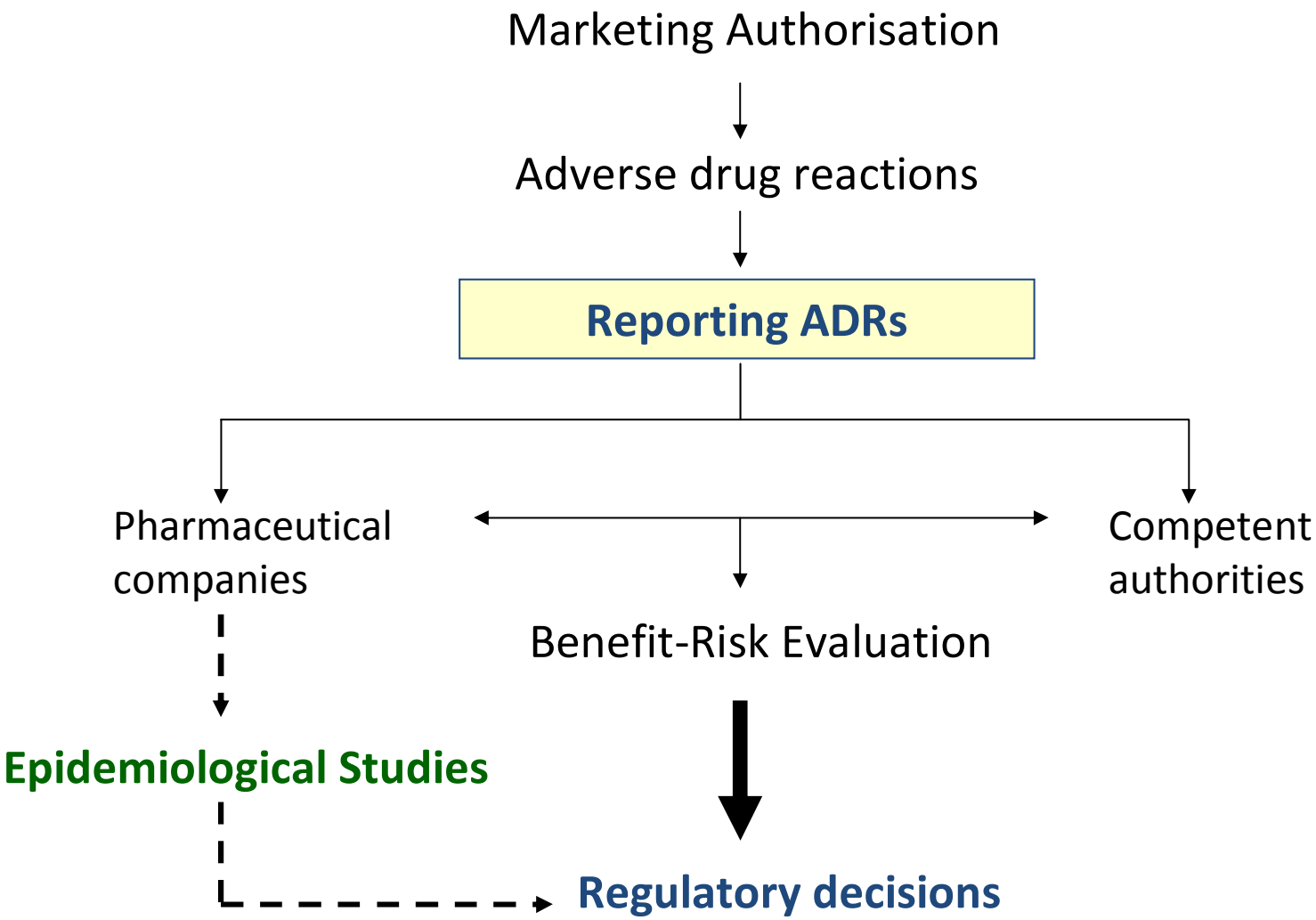
Stakeholders in Pharmacovigilance

- Competent authorities
  - National Pharmacovigilance Systems
- Pharmaceutical companies
- Healthcare professionals
- Consumers/Patients


Pharmaceutical companies
Actions
Patients
Healthcare professionals
Decisions
Evaluation
Information
Competent authorities
National and Supranational Pharmacovigilance Systems

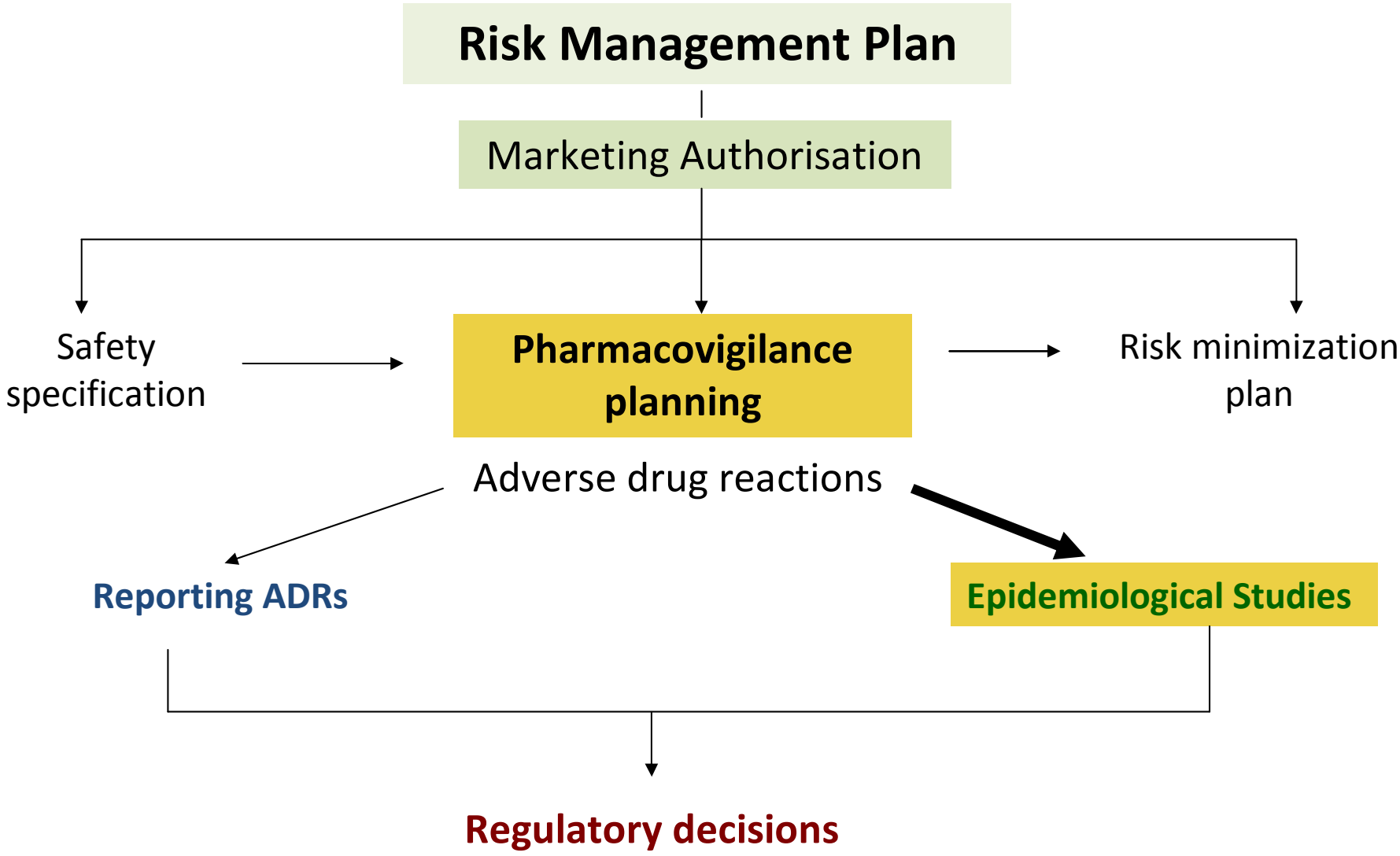
Models in Pharmacovigilance

Classical view: the reactive model



Models in Pharmacovigilance

Modern view: the proactive model



Risk Management Plan

- Aims
  - To anticipate potential safety issues
  - To carry out epidemiological studies
    - Raise signals as early as possible
    - Characterize the ADR (causality, susceptible populations, risk markers….)
    - Quantify the risk population impact
  - To implement risk minimization measures
    - Including effective risk communication
  - To check the effectiveness of measures adopted

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Biologicals

- Complex molecules
- Immune reactions are more likely with biologicals than with simpler chemical products
  - Lack of efficacy for neutralizing antibodies
  - Hypersensitivity reactions
- Immune reactions can occur with changes in the formulation / manufacturing process
  - PRCA associated with subcutaneous Eprex (Epoetin alfa) in chronic renal failure
    - Introduction of new stabilizer (polysorbate 80) + interaction with rubber uncoated plunger)

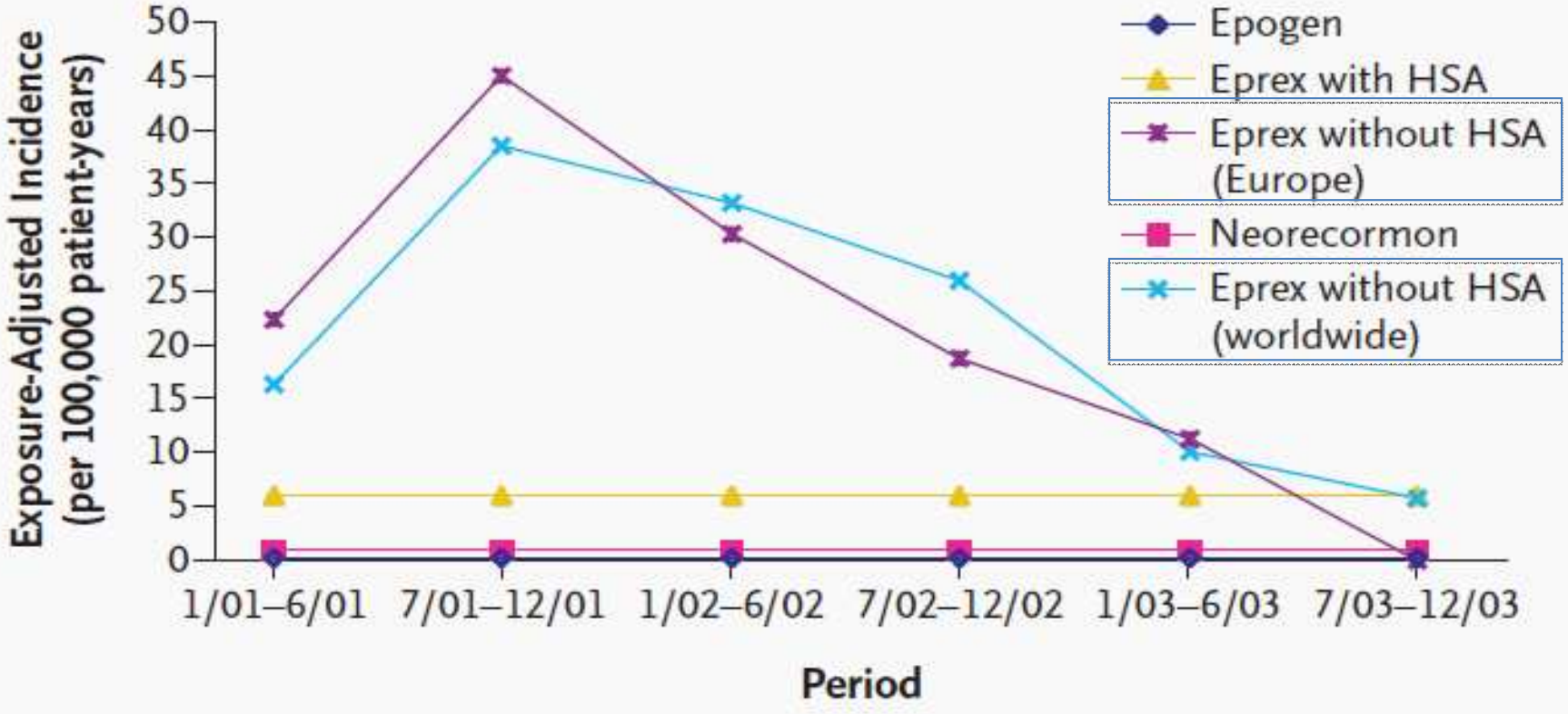

Figure 2. Estimates of the Worldwide Exposure-Adjusted Incidence of Epoetin-Associated Pure Red-Cell Aplasia According to the Product, between January 1, 2001, and December 31, 2003.

HSA denotes human serum albumin. Epogen is also marketed as Procrit, and Neorecormon as Recormon.

Bennet et al, NEJM 2004; 351: 1403-1408

Implications for biosimilars

- Immunogenic reactions of biosimilars may be different as those of the reference product
- Biosimilars are required to have a specific Risk Management Plan

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Agencia Española de Medicamentos y Productos Sanitarios - AEMPS | Notificación directa de Reacciones Adversas a Medicamentos

GOBIERNO DE ESPAÑA · MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD · agencia española de medicamentos y productos sanitarios

· Notificación de Profesional Sanitario

Paciente | Medicamento | Reacciones | Notificador

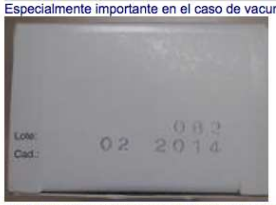
Información sobre el medicamento que ha podido causar la reacción adversa

Sospecha *

Medicamento *

Lote y fecha de caducidad

Especialmente importante en el caso de vacunas pero también con medicamentos biológicos (albúmina, inmunoglobulinas, anticuerpos monoclonales, interferones…).Ej 082 02/2014



En el caso de vacunas puede disponer de este dato en la cartilla de vacunación

Batch number required for biologicals

Motivo de la prescripción

Posología

Nº Dosis

Frecuencia

Vía de administración

Medidas Tomadas *

Fecha Inicio *

Fecha Fin

Grabar medicamento

Anterior Siguiente

Salir

ADRs associated to biologicals

- Can be different to other drugs
  - Infectious diseases
  - Cancer
  - Neurological diseases
- Difficult to identify and evaluate through case reports
- There is a need for epidemiological approaches

Automated databases

- Many safety issues nowadays are generated or evaluated using automated databases
- BIFAP is an automated database made up of 8 million people attended by general practitioners in Spain
  - The owner is the Spanish Agency for Medicines and Medical Devices
  - Similar to CPRD (UK), THIN (UK) or ICPC (NL)
- Problem: Most biological treatments are dispensed in hospitals and are not included in BIFAP, nor in many databases used in pharmacoepidemiology

GOBIERNO DE ESPAÑA · MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD · agencia española de medicamentos y productos sanitarios

BIFAP: Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria

Presentación

- Qué es BIFAP
- Misión de BIFAP
- Comité asesor
- Comité científico

Información a colaboradores

- Beneficios del colaborador
- Comunidades Autónomas participantes

Información a investigadores

- Solicitud de estudios a BIFAP

Actividad científica

- Proyectos de investigación
- Publicaciones científicas

Qué es BIFAP

BIFAP es una base de datos informatizada de registros médicos de Atención Primaria para la realización de estudios farmacoepidemiológicos, perteneciente a la Agencia Española del Medicamento y Productos Sanitarios (AEMPS), y cuenta con la colaboración de Comunidades Autónomas y el apoyo de las principales sociedades científicas implicadas.

BIFAP incluye la información aportada por 5.871 médicos de familia y pediatras de atención primaria del Sistema Nacional de Salud, integrando información de 8.077.841 historias clínicas anonimizadas válidas que suman un total de 46.194.650 personas-año de seguimiento (5,7 años de media de seguimiento por paciente), y que incluyen:

- 148.426.912 registros de problemas de salud.
- 817.430.834 registros de medicación.
- 25.125.580 registros de vacunaciones.
- 1.163.891.851 registros de datos generales del paciente.

http://www-bifap.org

Registries of exposed people to biologicals

- BIOBADASER
  - Registry of patients exposed to biologicals used in rheumatic diseases
  - Spanish Society for Rheumatology
  - Funding (Public-private)
    - Spanish Society for Rheumatology
    - Spanish Medicines Agency
    - Pharmaceutical companies
  - 35 hospitals
  - All relevant adverse events are recorded by participating rheumatologists
  - Phase II was closed in 2015 with more than 7,000 patients in the Registry

Biobadaser

https://biobadaser.ser.es

December 2015

Biobadaser
Sociedad Española de Reumatología

SPANISH REGISTRY ON ADVERSE EVENTS OF BIOLOGICAL THERAPIES IN RHEUMATIC DISEASES

(Phase II)

DECEMBER 2015 REPORT

Tamaño de fuente

pequeña normal grande

https://biobadaderm.fundacionpielsana.es/biobadaderm/index.html

Registro Español de tratamientos sistémicos en psoriasis.

El Registro Español de tratamientos sistémicos en psoriasis (BIOBADADERM) se puso en marcha en Octubre de 2008, como estrategia de farmacovigilancia en pacientes psoriásicos.

Ha sido promovido por la Fundación de la Academia Española de Dermatología y Venereología (FAEDV) en colaboración con la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) y las Unidades de Investigación de la FAEDV y de la Fundación Española de Reumatología (FER), siendo propiedad de la FAEDV. BIOBADADERM forma parte de Psonet: una red europea para compartir datos procedentes de registros de pacientes tratados con fármacos biológicos.

Sus objetivos son:

1. Identificar acontecimientos adversos (AA) relevantes que aparezcan durante el tratamiento con terapias biológicas, y estimar su frecuencia de aparición.
2. Identificar AA inesperados, en particular aquellos que pueden ocurrir tras periodos largos de exposición.
3. Identificar AA relevantes que aparezcan tras la suspensión del tratamiento.
4. Estimar el riesgo relativo de aparición de AA con terapias biológicas en pacientes con psoriasis. frente a pacientes psoriásicos expuestos a otros tratamientos sistémicos (no biológicos).
5. Identificar factores de riesgo de padecer AA con estos tratamientos.

Registries of exposed

- Objectives
  - Raise new signals
  - Quantify incidence of adverse events and confirm signals
  - Evaluate risk minimization measures
    - Infliximab and tuberculosis

BIOBADASER: *Incidence of tuberculosis in 2000*

	Incidence (100,000 person-years)	SMR (95%CI)
Biobadaser	1,893	90 (59-146)
EMECAR (RA patients not treated with anti-TNF)	95	4 (3-7)
General population	21	1

Gómez-Reino et al, Arthritis & Rheumatism 2003; 48:2122-2127

Conclusions

- Pharmacovigilance should be as proactive as possible
  - Risk Management Plans
- Biologicals have specific features that make pharmacovigilance (and particularly its proactive concept) even more important
- Spanish pharmacovigilance System is well-prepared for the challenge of biologicals, but complementary epidemiological approaches would be very convenient, such as Registries of Exposed (the successful experience of Biobadaser / Biobaderm shows a road map to follow).