EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Risk Management: Safety Specification

Identification and Methodologies

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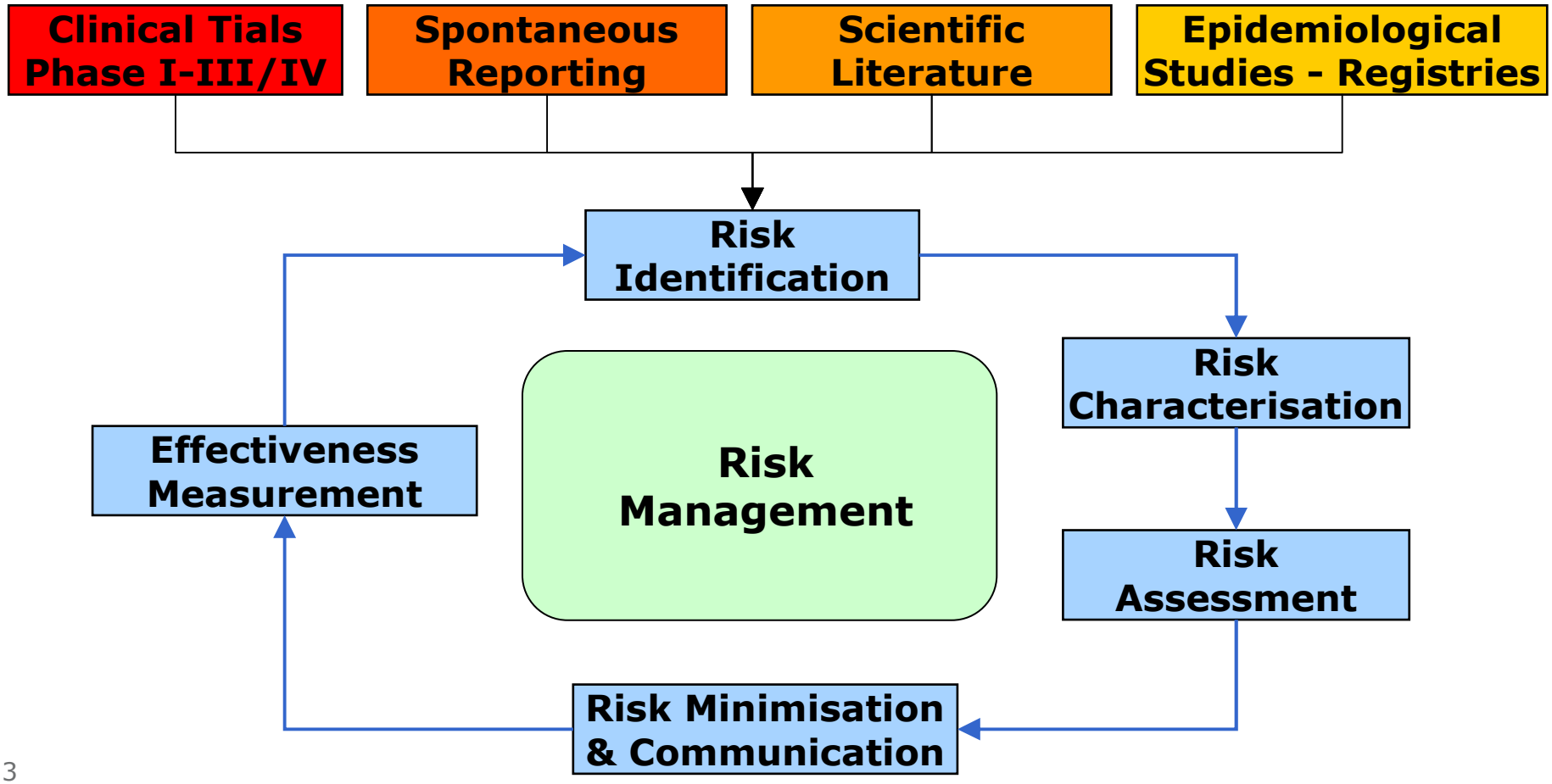
An agency of the European Union

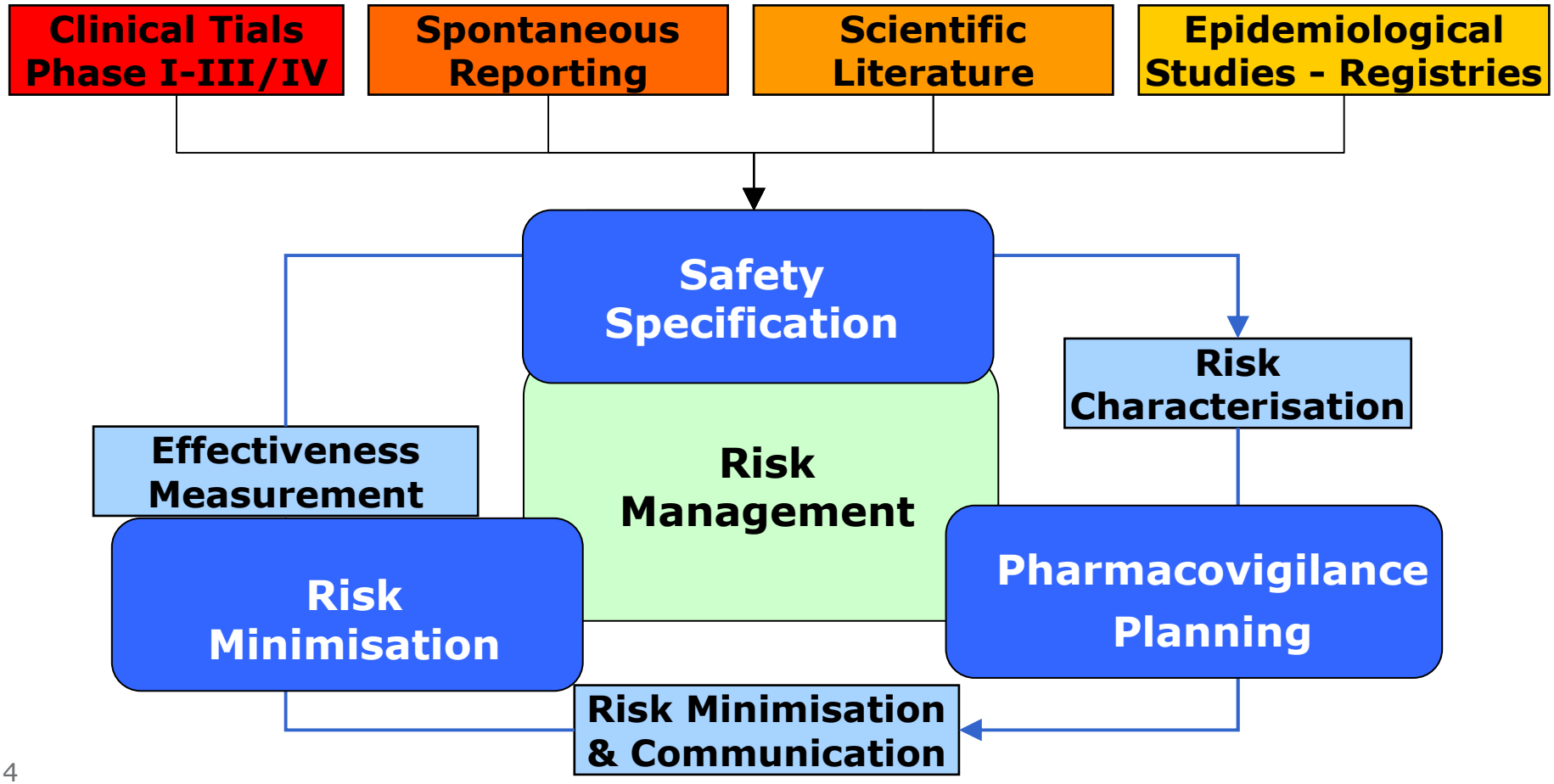
Agenda

1. Introduction to EU Risk Management Plan
   - Structure of EU-RMP, legal frame
2. Nanomedicines Risk Characterization
   - Purpose of nanotechnology
   - Physical-chemical characteristics, route of admin, quality
   - Pharmacokinetic, chemical reactivity
   - Biodegradability, toxicity
3. EU-RMP Template
   - Current elements
   - Nano-specific elements

The Risk Management Cycle



The Risk Management Cycle



EU Legislation on Risk Management

- Article 8 (3)(ia) of Directive 2001/83/EC as amended by Directive 2004/27/EC

  The MA application shall be accompanied by…a detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.

- Article 9(4)(c) of Regulation (EC) No 726/2004

  Requires details of conditions and restrictions on supply or use or with regard to safe and effective use of the medicinal product attached to Opinion

- ICH E2E Guideline on Pharmacovigilance Planning
- CHMP Guideline on Risk Management Systems (EMEA/CHMP/96268/2005)
- EU Risk Management Template (EU-RMP) (EMEA/192632/2006)

} Volume 9A of the Rules Governing Medicinal Products in the European Union

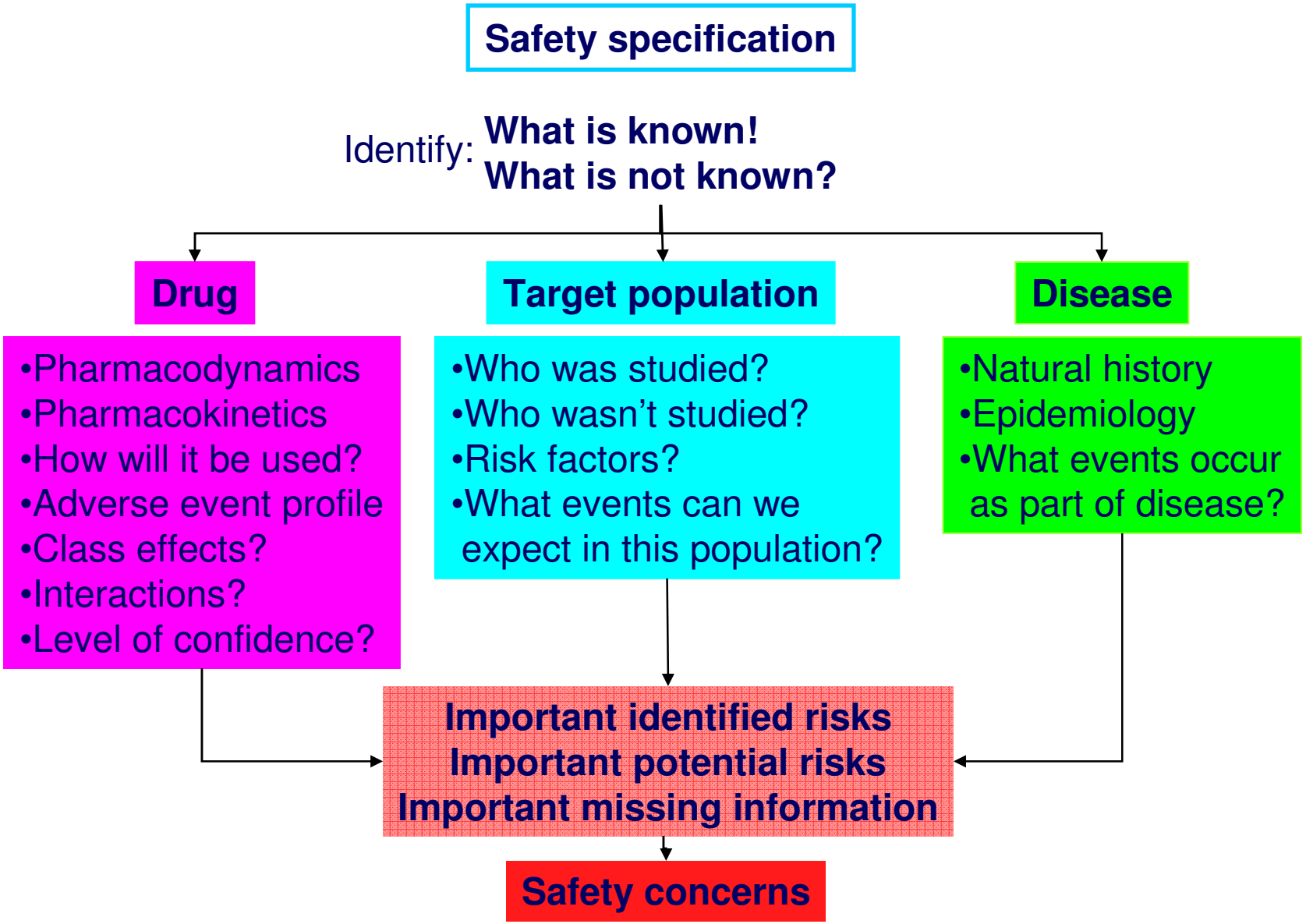
EU-RMP Structure

Part I

- **Safety Specification** (ICH E2E)
  - + Additional EU-specific requirements
- **Pharmacovigilance Plan** (ICH E2E)

Part II

- **Evaluation** of need for additional risk minimisation activities
  - **Risk Minimisation Plan** (if needed)
  - **Effectiveness** of Risk Minimization Measures


Safety specification
Identify:
What is known!
What is not known?
Drug
•Pharmacodynamics
•Pharmacokinetics
•How will it be used?
•Adverse event profile
•Class effects?
•Interactions?
•Level of confidence?
Target population
•Who was studied?
•Who wasn't studied?
•Risk factors?
•What events can we expect in this population?
Disease
•Natural history
•Epidemiology
•What events occur as part of disease?
Important identified risks
Important potential risks
Important missing information
Safety concerns

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Concepts applicable to nanomedicines

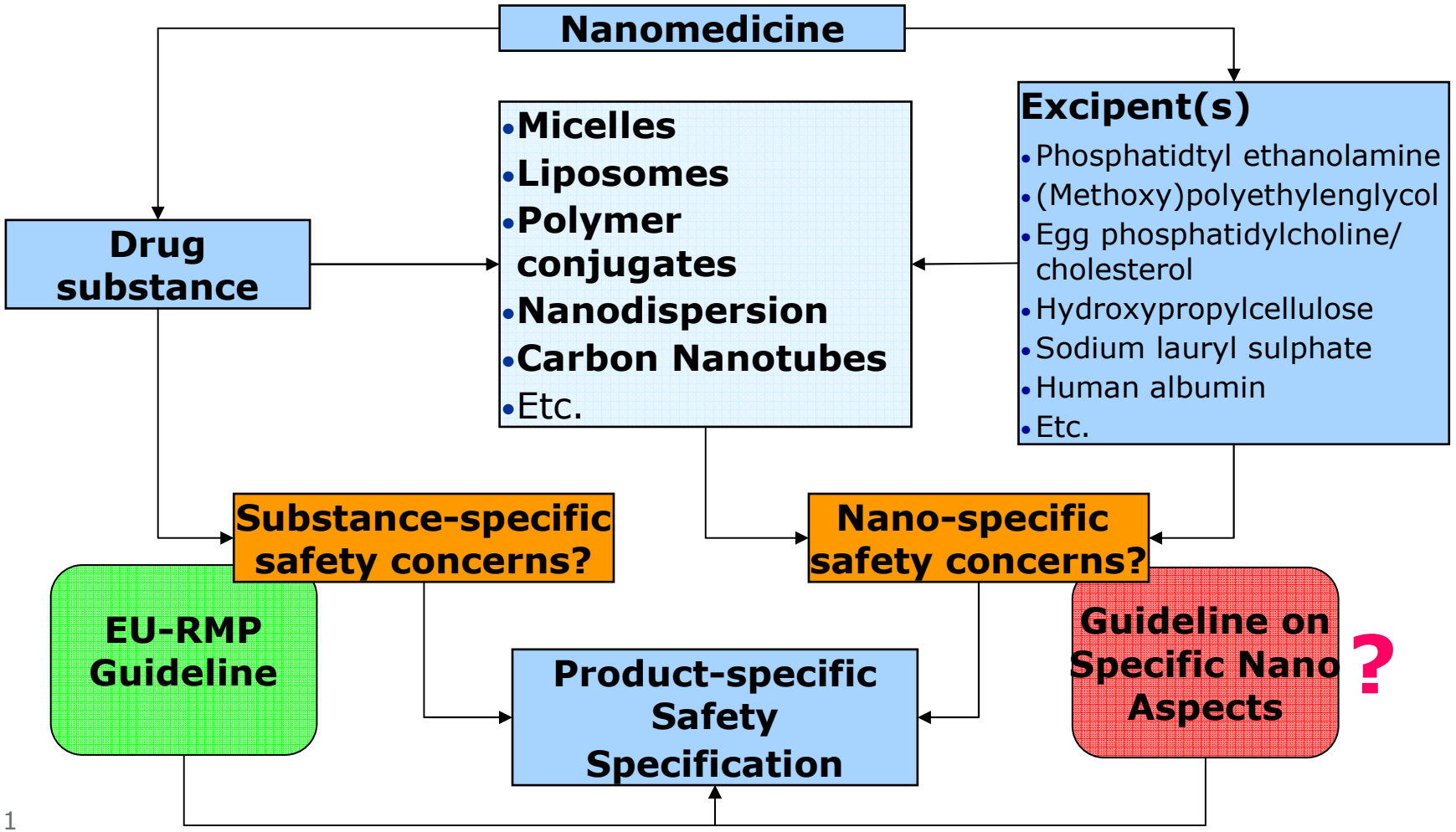
- Specific properties in nano-scale range

- Purposely-designed nanomaterials

Examples of Nanotechnology Medicines

Medicinal product	Nanotechnology purpose
Abraxane (paclitaxel)	Solvent free colloidal suspension of albumin-bound nanoparticles to increase water solubility
Caelyx (doxorubicin)	Pegylated liposome to increase blood circulation (long acting)
Emend (aprepitant)	Colloidal dispersion of nanoparticles to increase bioavailability (wet milling method)
Mepact (mifamurtide)	Liposome encapsulation to facilitate activation of macrophages
Myocet (doxorubicin)	Liposome encapsulation to reduce cardiac toxicity and to increase tumor tissue distribution
Rapamune (sirolimus)	Colloidal nanodispersion stabilised with poloxamer to reduce particle size for increased stability and bioavailability

Reflection on safety aspects



Nanotechnology - Purposes

Encapsulation techniques •Micelles •Liposomes (+ polymer ligands) •PEG-ylation (coating)	• Nanodispersion for improved drug solubility (increased bioavailability) • Surface modification to avoid agglomeration (PK) • Encapsulation (decreased toxicity) • Nanocarriers for targeted drug delivery or controlled drug release (cancer treatment) • Biomarkers for treatment and/or imaging systems (cancer treatment) • Bioactive polymer (inherent activity) conjugation
Polymer conjugated •Polyethylenglycol (PEG) •Polyglutamic acid (PGA) •Hydroxypropylmethacrylamide (HPMA) •Alginates •Chitosan •Dendrimers	
Nanocarrier •Carbon nanotubes **?**	

Nanomedicines Risk Characterisation

- **Physico-chemical characteristics**
  - Particle size and size distribution of free particles and agglomerates
  - Polymer heterogeneity defined by ratio of weight/number average molecular weight (mono- or polydispersity)
  - Structure and aspect ratio
  - Specific surface area (SSA)
  - Surface morphology/absorption properties, surface charge
  - Stability (aggregation/dissolution/agglomeration/release from encapsulation)
  - Solubility (octanol-water coefficient) determines release rate in biological system
  - Hydrophilic/lipophilic balance

Nanomedicines Risk Characterisation *continued*

- **Route of administration**
  - Oral
  - Topical
  - Intravenous/intramuscular/sub-cutaneous
  - Inhalation
- **Quality aspects**
  - Purity (chemical/polymer impurities and residual solvents)
  - Manufacturing intermediates/pre-cursors
  - Stability
  - Sterility

Nanomedicines Risk Characterisation *continued*

- **Pharmacokinetic aspects**
  - Human exposure during entire life-cycle (including production, storage, distribution, waste disposal)
  - Cell/tissue/whole body distribution
  - Bioaccumulation (biopersistence) and organ toxicity
- **Chemical reactivity**
  - Photo-activation (radical formation, oxidation/reduction) e.g. if topical use
  - In-vivo release of reactive oxygen species (ROS)
  - Asbestos-like properties of biopersistent, rigid, high aspect ratio nanoparticles associated with inflammation, granulomas etc.

Nanomedicines Risk Characterisation *continued*

- **Biodegradability**
  - Dependent on route of administration (enzymes of GI tract have different effect than those of plasma/extracellular fluids)
  - Time-dependent rate of degradation and location of degradation products (whole body/intracellular)
  - Are degradation products toxic or immunogenic?
  - If not biodegradable (e.g. PEG, HPMA conjugates) the polymer must be small enough for renal clearance

=>**Need for validated characterisation methods based on GMP and GLP standards**

Biodistribution

	Methodology
PK cellular uptake	• Fluorescence labelling (polymers), but no validated assays • Radiolabelling (polymers) • Quantitative HPLC assay

PK whole body distribution	• Radiolabelled polymers/dissection analysis
	• Whole body autoradiography
	• Gamma camera imaging (animals and man)
	• Non-invasive
	  • Magnet resonance imaging (MRI)
	  • Positron emission tomography (PET)
	  • HPLC assays

Pre-clinical safety/efficacy screening	• Biomarker assays (e.g. target receptor screening)

Toxicity Screening

- **In-vitro screening**
  - Cytotoxicity with different cell lines (also of degradation products)
  - Haematocompatibility (haemolysis, complement activation)
  - Hydrolytic/enzymatic degradation rate (pH dependent)
  - Scanning Electron Microscopy for changes to cell morphology
  - Genotoxicity (Comet-, Micronucleus-, Gene Mutation Assay; Ames test)
- **In-vivo screening**
  - Antigenicity (IgG, IgM production)
  - Immunogenicity (cytokine and chemokine induction)
  - Dose-dependent body distribution (short-/long-term)

=>**Need for assays with *in-vitro—in-vivo* correlation**

How to Address Deficiencies?

- Comparison of new 'nanomedicine' with conventional medicinal product of same active ingredient (e.g. Paclitaxel/Doxorubicin)
- Likelihood to cause harm at each life-cycle stage
- Is relevant toxicity data available from other areas? (e.g. asbestos)
- Likelihood of exposure and likelihood of effects and severity?

Nanomedicines Associated Risks (I)

Potential effects at cellular/intracellular level:

- Haemolysis (haemoglobin release)
- Embolism through platelet/red-blood cell aggregation and associated cardiovascular effects
- Infusion related reactions by complement activation (also through colloidal osmotic effects) e.g. poloxamer 188 and PEG
- Accumulation of non-biodegradable polymers (lysosomal storage-like disease syndrome)
- Nanoparticle-mediated modulation of cellular efflux-pumps
- Nanoparticle-mediated gene expression
- Induction of oxidative stress (also to exhibit targeted antitumor effect)

SCENIHR Opinion on Risk Assessment of Products of Nanotechnologies 2009
Gaspar RS, Duncan R, Adv Drug Deliv Rev. 2009 Nov 12;61(13):1220-31

Nanomedicines Associated Risks (II)

Potential effects at cellular/intracellular level:

- Inflammation associated with granulomas (mouse model); e.g. pulmonary inflammation associated with inhalation of single walled carbon nanotubes
- Protein-fibrillation: in-vitro tests showed that nanoparticles may increase the risk of nucleation of human $beta_2$-microglobulin fibrils to form amyloid; but currently there is no *in-vivo* data available
- Pleural mesothelioma associated with biopersistent, rigid, long fibre like nanoparticles with high aspect ratio (fibrous-type or asbestos-like effect)

Nanomedicines Associated Risks (III)

Potential pharmacokinetic effects:

- Particle translocation
  - Brain translocation after inhalation, blood-brain barrier crossing
  - Skin epithelium translocation with topical use may be limited due to pore size at tight junctions (0.3 – 1.0 nm)
- Organ distribution (lungs, testes, brain, kidney, liver, spleen)
  - The smaller the particle size the higher were organ concentrations in mice
  - After i.v. administration smallest particles showed most widespread organ distribution with larger particles found mostly in liver and spleen (rat)

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EU Risk Management Plan Template

0 Product information

1 Safety Specification

2 Pharmacovigilance Plan

3 Evaluation of the need for risk minimisation activities

4 Risk Minimisation Plan

5 Summary of the EU-RMP

6 Contact person details

Annexes 1 - 8

To be valid the EU-RMP must contain:
1. Safety Specification
2. Pharmaovigilance Plan
3. Evaluation

Safety Specification – Non Clinical ICH E2E

1.1 Safety concerns not adequately addressed

- Toxicity
  - Repeat-dose toxicity
  - Reproductive/developmental toxicity
  - Nephrotoxicity
  - Hepatotoxicity
  - Genotoxicity
  - Carcinogenicity etc
- General pharmacology (cardiovascular including QT prolongation, nervous system etc.)
- Drug interaction mechanisms
- Other toxicities, **including nano-specific**
- Need for additional non-clinical data in special populations

Safety Specification – Clinical

ICH E2E

1.2 Limitation of human safety database

- Clinical trials (blinded RCT - all CT population)
  - Broken down by duration, dose, age group, gender, ethnic origin, special populations
- Epidemiological studies
- Post-marketing studies (if any)
  - Broken down by dose, age group, gender, country, other demographic factor

Safety Specification – Clinical

ICH E2E

1.3 Populations not studied in pre-authorisation

- Exclusion criteria for pivotal and supporting studies
  - Number of exposed patients
  - Age range
  - Children
  - Elderly
  - Pregnant / lactating women
  - Co-morbidities
  - Different disease severity
  - Genetic polymorphisms
  - Ethnic origins

Safety Specification – Clinical

ICH E2E

1.4 Post-authorisation experience

- Projected usage data: estimated population drug use over time in treatment and market position
- Actual usage data: differences real vs predicted exposure patterns, off-label use
- Regulatory actions taken

Safety Specification – Clinical

ICH E2E

1.5 Adverse events – identified and potential risks

- MedDRA coding
- Seriousness/outcomes
- Severity, nature of risk
- Frequency (95% CI)
- Background incidence/prevalence
- Risk groups and risk factors
- Potential mechanisms
- Preventability
- Public health impact
- Evidence source
- Regulatory action taken

Safety Specification – Clinical

ICH E2E

1.6 Identified and potential interactions

- Effect of interaction
- Evidence source
- Possible mechanism
- Potential health risk

Safety Specification – Clinical

ICH E2E

1.7 Epidemiology of indication(s) and important adverse events

- Incidence
- Prevalence
- Mortality
- Potential health risk
- Demographic profile target population (age/sex distribution)
- Co-morbidities of target population

Safety Specification – Clinical

ICH E2E

1.8 Pharmacological class effect

- Class common identified risks
- Justification if not considered a risk
- Including nano-specific class effects once established over time

Safety Specification

EU

1.9 Additional EU Requirements

- Potential for overdose
- Potential for transmission of infectious agents
- Potential for misuse for illegal purposes
- Potential for off-label/off-label paediatric use
- Potential risks with regard to applied nanotechnology
  - Immunogenicity
  - Tumorgenicity
  - Inflammatory diseases
  - Protein-fibrillation (amyloidosis)
  - Cardiovascular risks
  - Bioaccumulation (long term safety)
  - Parent-child transmission
  - Environmental risks etc.

Safety Specification

ICH E2E

1.10 Summary of the Safety Specification

- **Important identified risks**
- **Important potential risk**
- **Important missing information**

The Safety Specification is the basis for

- Pharmacovigilance Plan (Part I)
- Evaluation of the need for additional risk minimisation activities (Part II)

In Summary…

Checklist for nano-specific risks (I)

- Quality characteristics of final product (composition, purity, biological activity of nanoparticles, etc.)
- Storage and distribution (stability)
- Administration procedures (polymer scaffoldings, surgical procedures, patient conditioning, diagnostic procedures, co-medication, etc.)
- Interactions medicine/patient (immunogenicity, tumorgenicity, inflammation, protein-fibrillation, cardiovascular risks etc.)
- Polymers, scaffolds, matrices, lyposomes, nanodispersions, (biodegradation, bioaccumulation, organ toxicity etc.)

Checklist for nano-specific risks (II)

- Biopersistence of nanomaterials (and degradation products) (lysosomal storage-like disease syndrome, malignancy, autoimmunity, escape procedures, long-term safety)
- Re-administration (immune reactions, anaphylaxis, repeated surgical procedures, etc.)
- Parent-child transmission (foetal, transmammary, germ line effects)
- Environmental exposure
- Specific risks which do not fit in existing sections of EU-RMP could be discussed as a new section under 'Additional EU Requirements' (as for EU-RMPs for ATMPs)

Conclusion

- Because of their novelty, complexity and technical specificity nanomedicines may imply new, unknown risks to patients
- New Guidance would support a comprehensive description of nano-specific risks in the Safety Specification which is the basis for a sound risk management system (Pharmacovigilance and Risk Minimisation Planning)

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Thank you for your attention!

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