PharmInvent

Pharmacovigilance and Risk Minimisation Plans for Nanomedicines

1st International Workshop on Nanomedicines
European Medicines Agency

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"Nanomedicine has unbelievable transformational potential, but we must be as brave, persistent and smart as the biotechnology innovators were when that field was emerging 20 years ago."

Ferrari, M, In: Gewin, V: Big opportunities in a small world, Nature, 460:540-1

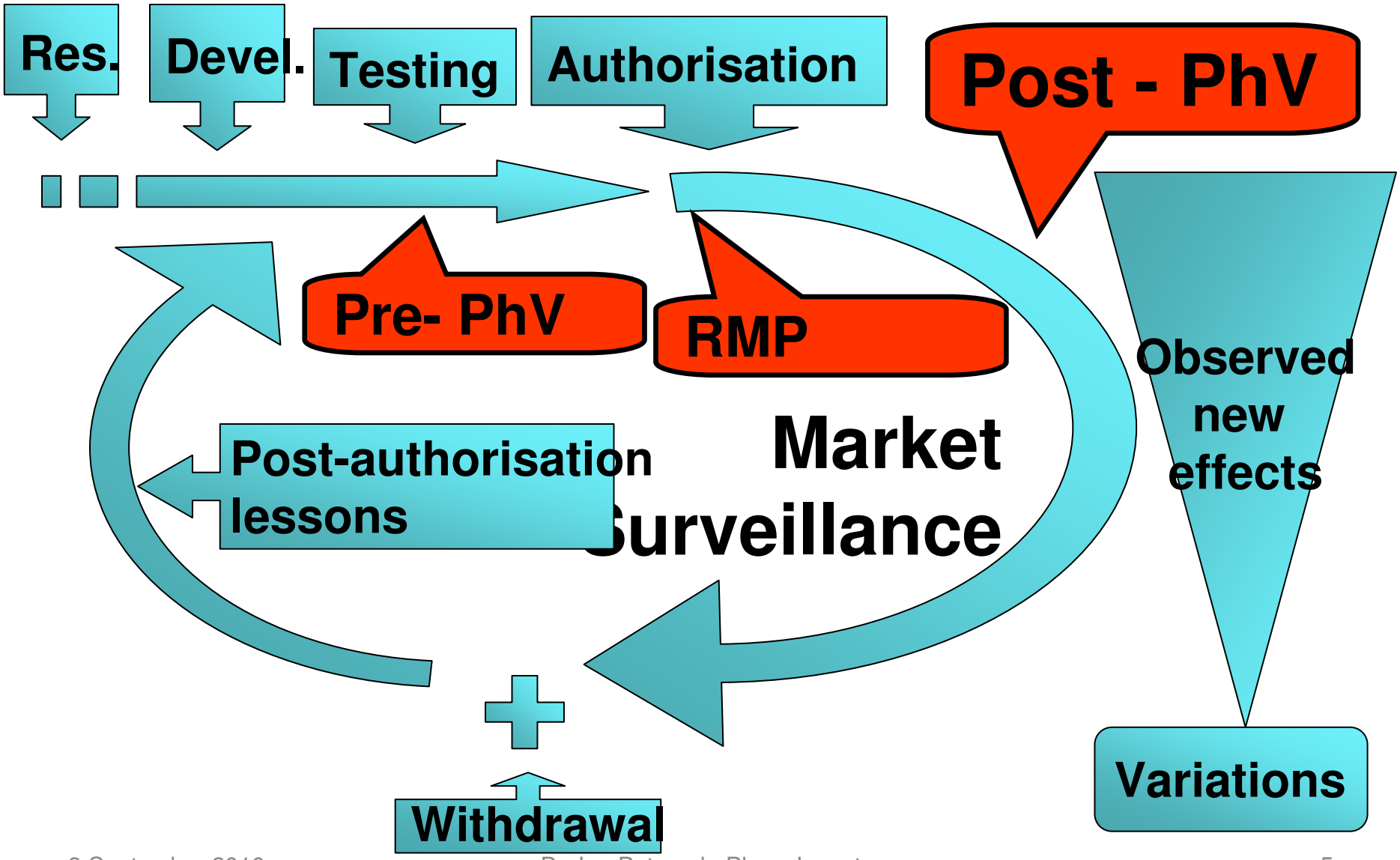
Anything
that can go wrong,
will go wrong.

Murphy's law

In this talk

- How to
  - plan pharmacovigilance
  - plan risk minimisation
- for nanomedicines
- in pre and post-authorisation

PhV Timing in a med. product lifecycle



Pre-clinical safety testing

Risk Management priorities:

- Controlled and isolated facilities to prevent human exposure as well as any leak of the tested nanomaterials to environment
- Does not need to be described in the EU-RMP as a risk minimisation (not related to administration to patients)

Clinical Trials – Phase I

- For Phase I see the *Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products*
- High-risk products: "*when there are concerns that serious adverse reactions in first-in-man clinical trials may occur*" = almost always

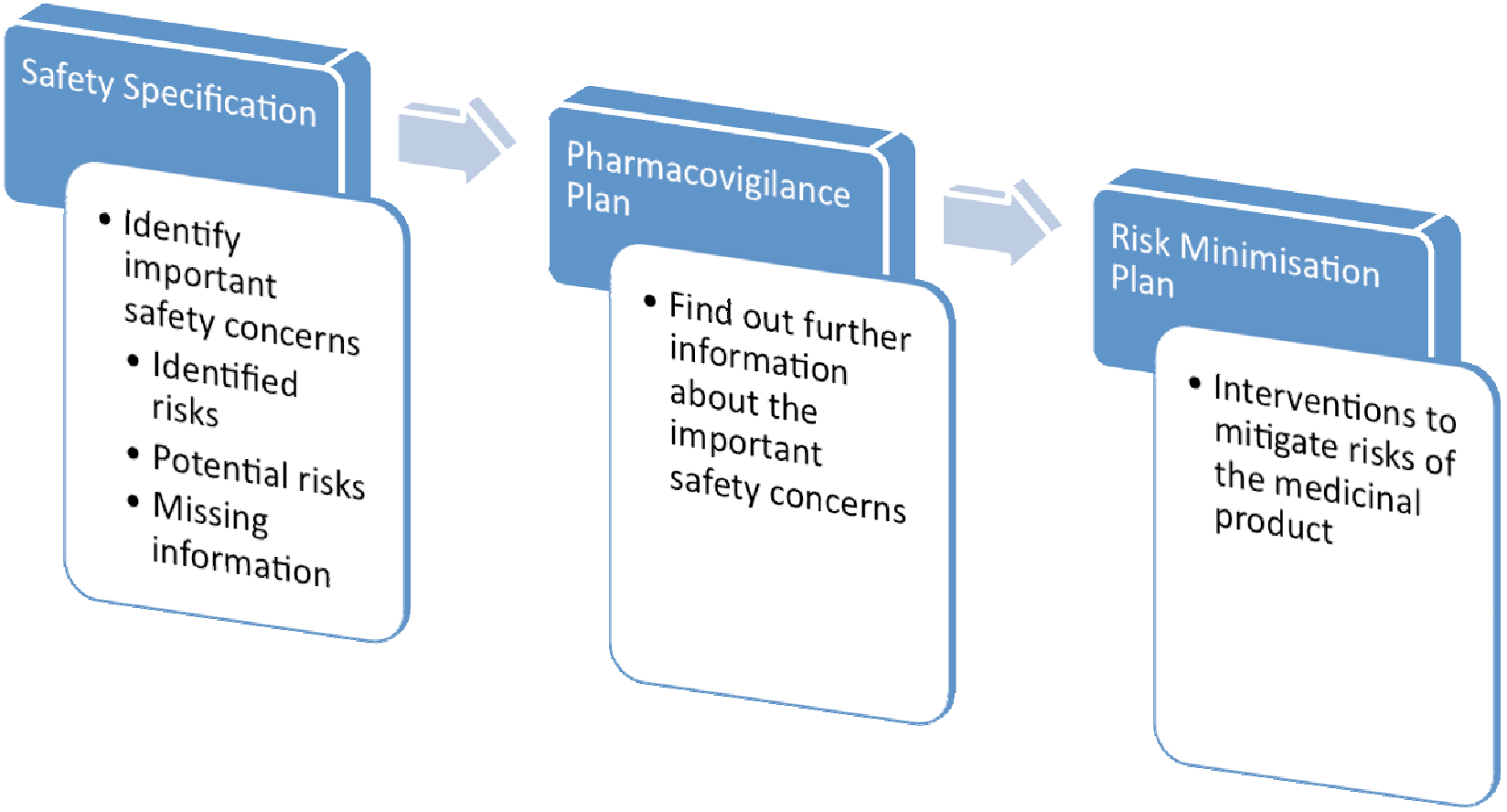
Clinical Trials

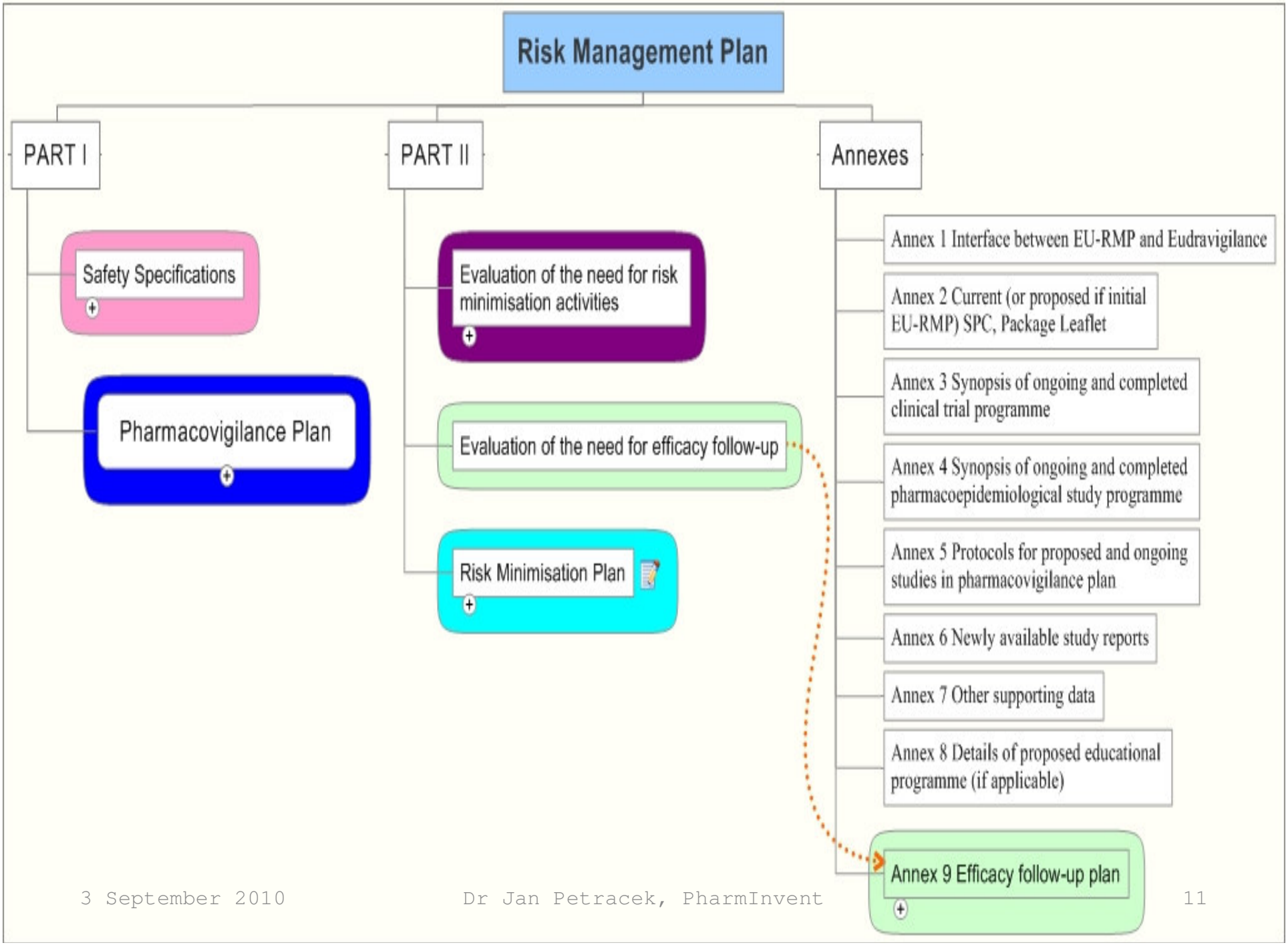
- Development risk management plan is only a recommendation so far
- GCP principles and approval process of individual trials usually suffice for good management of risks to both subjects and environment
- Development Safety Update Reports (ICH E2F) provide framework for summary of important risks that would create a basis for post-authorisation risk management

Pre-submission planning

- Early consultation with the Agency about the draft risk management plan
- Scientific advice available for the overall EU-RMP structure, as well as for the studies to be included in the plan
- Well drafted EU-RMP will save time during the application evaluation

General EU-RMP philosophy




Risk Management Plan
PART I
PART II
Annexes
Safety Specifications
Pharmacovigilance Plan
Evaluation of the need for risk minimisation activities
Evaluation of the need for efficacy follow-up
Risk Minimisation Plan
Annex 1 Interface between EU-RMP and Eudravigilance
Annex 2 Current (or proposed if initial EU-RMP) SPC, Package Leaflet
Annex 3 Synopsis of ongoing and completed clinical trial programme
Annex 4 Synopsis of ongoing and completed pharmacoepidemiological study programme
Annex 5 Protocols for proposed and ongoing studies in pharmacovigilance plan
Annex 6 Newly available study reports
Annex 7 Other supporting data
Annex 8 Details of proposed educational programme (if applicable)
Annex 9 Efficacy follow-up plan

Pharmacovigilance Plan

- Designed to learn more about safety profile of a medicine in post-authorisation phase
- In addition to routine pharmacovigilance system, intensive monitoring schemes, observational trials as well as interventional trials and pre-clinical studies may be included in the pharmacovigilance plan

Pharmacovigilance plan elements

Action plan for safety concerns:

- Safety concern
- Objective of proposed actions(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the MAA/MAH for safety concern and proposed actions
- Milestones for evaluation and reporting

Evidence gathering in pharmacovigilance plan of "high risk products"

- Pragmatic trials
- Randomised trials in individual patients
- Adaptive design trials (while respecting the regulatory requirements)
- Long term non-interventional trials, including patient registries

Risk Minimisation Plan(1)

- Only needed if additional risk minimisation activities needed
- Should list safety concerns and discuss which risk minimisation activities needed for each concern
- Should include both routine and additional risk minimisation activities

Risk Minimisation Plan(2)

Action plan for safety concerns

- Safety concern
- Objective and rationale of proposed actions(s)
- Proposed actions
- Criteria to be used to verify the success of proposed risk reduction actions
- Proposed review period

Risk Minimisation Tools (examples)

1. Provision of information
   - Routine communication docs – labelling
   - Specific (additional) - Educational plans
   - Informed consents
2. Control of the use of medicine
   - Legal status of a medicine
   - Restricted access programs
   - Control of prescription size or validity

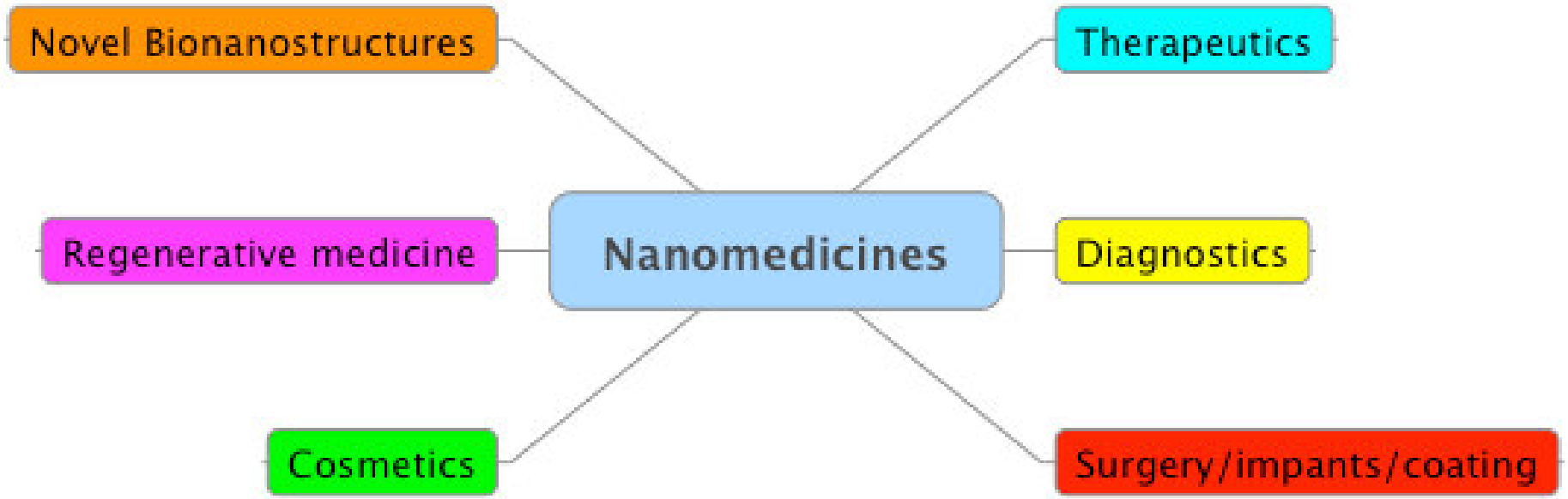
Efficacy Follow-up System

- Both interventional and non-interventional designs
- May measure “real-life” specificity and sensitivity of mandated tests
- Typically may include studies of long-term effectiveness, as well as studies of risk minimisation effectiveness (e.g., how well the trained physicians are using the medicines).

Measuring Effectiveness of Risk Minimisation Tools

- Conditio sine qua non
- Adaptation of the activities based on the measurements
- Examples:
  - Comparison of healthcare provider sites
  - Tests and questionnaires
  - Registries

Possible categorisation of "nanomedicines products"



Ref:
http://www.observatorynano.eu/project/filesystem/files/Executive%20summary%20April%202009.pdf

An individual product needs an individual EU-RMP

- Varieties in the nanotechnology applications in medicinal products make it impossible to apply one approach for all
- However, current flexibility of the EU-RMP allows for accommodation of this variability

Nanotechnology approach may be seen as a risk minimisation activity

- EU-RMP safety specification works with the toxicity of active substance, so a delivery system that enables toxicity reduction can be presented as a risk minimisation activity (e.g., for drugs like daunorubicin, doxorubicin, amphothericin B)
- Reduction of toxicity originally caused by solvents or other excipients (e.g. paclitaxel in Abraxane)

New toxicity concerns of drug delivery systems

- The major toxicity usually discovered in pre-clinical studies and clinical trials prior to authorisation
- Examples – carbon nanotubes, nanohorns, nanodiamonds…
- **Long term safety follow-up** is likely to be required for these delivery systems

Drug Delivery System Failure – New Type of Potential Risks

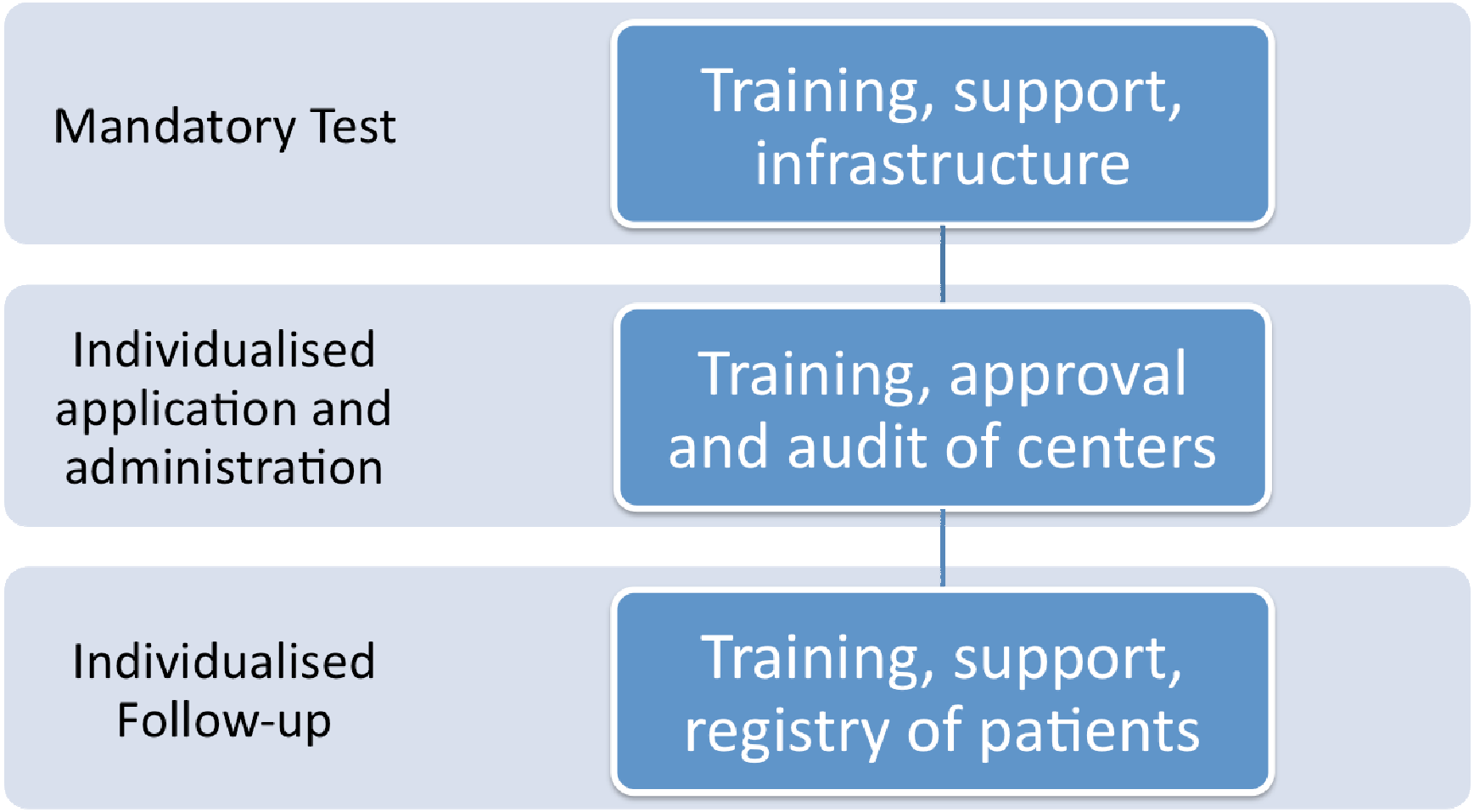
- For example with magnetoliposomes, micro-bubble based delivery systems, nanoshells…)
- Include potential of medical errors caused by physicians, or errors caused by a medical device failure (MR, ultrasound, other release control systems…)
- Training programs, rescue procedures, early warning systems and barriers to errors should be considered

Shift from one-size-fits-all towards personalised medicines

- Are there models within personalised medicines paradigm that could be economically as appealing as the blockbuster approach?
- Nanotechnology enables both - better understanding of intracellular functions and its targeting by therapeutics – excellent possibilities for personalisation

Risk Management framework could make the effective personalisation of therapy possible while maintaining revenues of a blockbuster!

EU-RMP mandated personalisation



Conclusions 1

- The current EU-RMP framework is flexible enough to accommodate nanomedicines specific risks
- Higher use of efficacy follow-up systems, novel designs of trials included in the pharmacovigilance plan, and number of additional risk minimisation measures might be anticipated
- The application of nanotechnology itself may also work as a risk minimisation tool

Conclusions 2

- Closer links with Environmental Risk Assessment might be needed, most likely in the form of common instructions and trainings for users of the medicinal products
- EU-RMP may facilitate personalisation of therapy while maintaining some attributes of blockbusters
- EU-RMP is the way to further improve benefit/risk balance of any high-risk medicine

Thank you for your attention

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