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.”

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

Res.  Devel.  Testing  Authorisation  Post - PhV

Pre- PhV  RMP  Observed new effects

Post-authorisation lessons

Market Surveillance  Variations

Withdrawal

3 September 2010
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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

- **Safety Specification**
  - Identify important safety concerns
  - Identified risks
  - Potential risks
  - Missing information

- **Pharmacovigilance Plan**
  - Find out further information about the important safety concerns

- **Risk Minimisation Plan**
  - Interventions to mitigate risks of the medicinal product
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

Mandatory Test

Training, support, infrastructure

Individualised application and administration

Training, approval and audit of centers

Individualised Follow-up

Training, support, registry of patients
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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