Aspects of Pharmacovigilance in Neonates

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Aspects of Pharmacovigilance in Neonates

Points to consider

- **Guidelines**
- **Challenge**
- **Target population**
- **Pharmacovigilance tools**
- **Present situation**
- **Further development**

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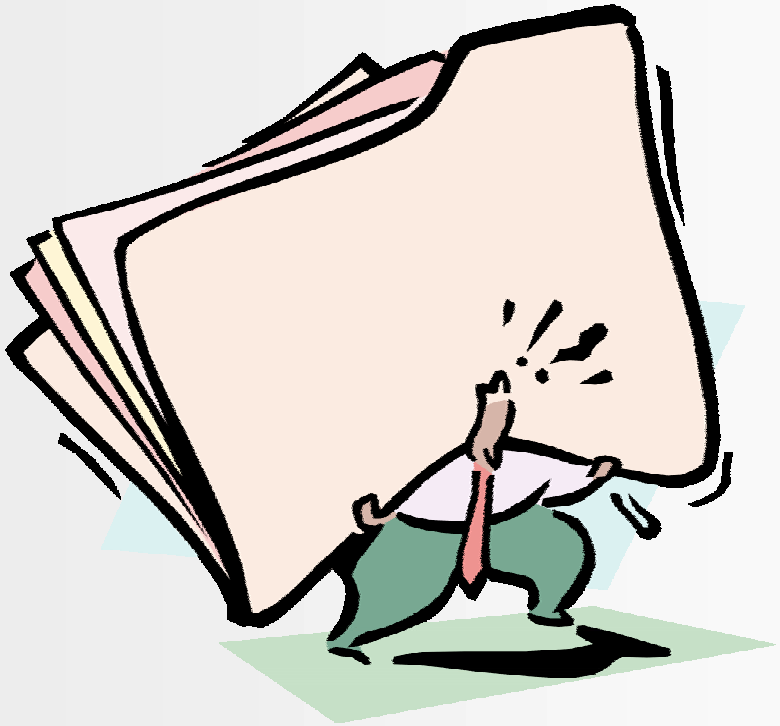
EU - legislation and Guidelines



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Guidelines (ICH, CHMP)

- **Guideline on conducting trial in small population**
- **Guideline on Pharmacovigilance in Paediatric population**
- **Guideline on Risk Managemant Plan and Pharmacovigilance Plan**
- **Guideline on the Need for Pre-clinical Testing of Human Pharmaceuticals in Juvenile Animals**
- **Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11)**
- **draft guidelines many more to come with respect to neonates**

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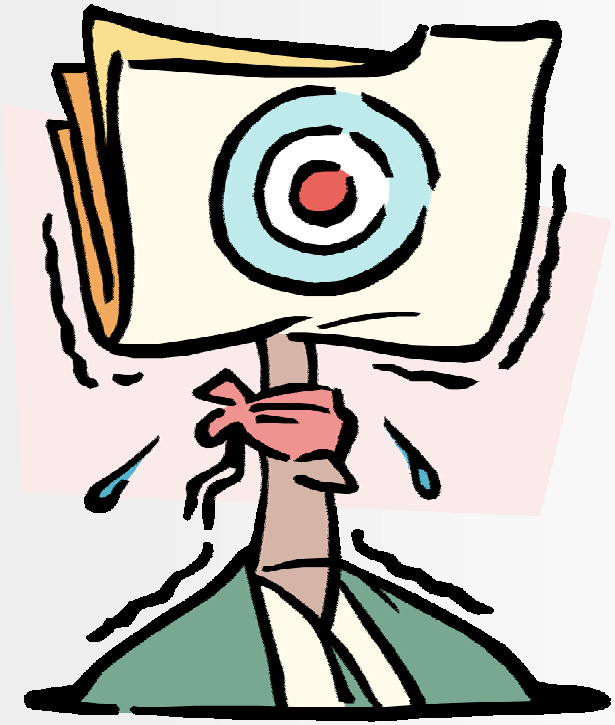
Target population



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Target population

- **Neonate periode is covering the age range 0 - 28 days post delivery.**
- **The neonate may by differentiated into**
  - **preterm (before 37 weeks gestation)**
  - **term infant (from 37 – 42 weeks gestation)**
  - **Post term (after 42 weeks gestation)**
- **Approximately 50 - 90% of drugs used for treatment in the paediatric population are not authorised**
- **Usage of those drugs is mainly related to neonatal intensive care treatment, approximately 3 – 5% of all newborn will tent to be multi drug users**

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Target population

- **perinatal complication**
  - **meconium aspiration, metabolic disease, respiratory adaptation problems, infection, nutrition**
- **Congenital disease/ malformation**
  - **CNS, heart malformation, intestinal- or intrathoracic (diaphragmatic hernia, malrotation), coagulation, haematological**
- **acquired Disease**
  - **Coagulation, metabolic, infection, respiratory**

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Target population

Neonates ≠ Rarely problems with drugs

Neonates => Indication and dosage

Neonates => appropriate formulation

Neonates => Organ impairment

Neonates => small numbers to be treated

Neonates => Multifactorial Pharmacovigilance

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Challenge

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Challenge

- **trials enrolling several hundred patients may not be practical or possible in most cases and even common adverse reaction may not be detectable.**
- **In particular, if there is a latent period before onset or a trigger such as a change in growth, maturation or development.**
- **Conducting, analysis, and interpretation of studies within the neonatal population may at times be constrained by the prevalence of the disease and varying degrees (e.g. neurometabolic disease)**
- **increased effort to conduct pharmacovigilance in pre and post authorisation period**

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Challenge

- **Long-term follow up is important for designated treatment and is essential for capturing effects on skeletal, neural, behavioural, sexual and immune maturation and development.**
- **Pathophysiological knowledge of organ function supported by juvenile animal toxicology studies, mutagenicity and carcinogenicity data**
- **Assessing a risk management plan (RMP) and Pharmacovigilance Plan (PP) in view of proposed indication or usage in the neonate population.**

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Challenge

- **The benefit/ risk assessment may be significantly different depending on the indication for which the product is used and may be influenced by the availability of other therapeutic options available.**
- **Long-term benefit/ risk may be in contradiction to the benefit/ risk assessment at time of drug administration**
- **extrapolation of experience from Adult to neonates is not feasible with respect to different indication**
- **Monitoring ADRs with laboratory values may be very difficult due to lack of normal ranges information**

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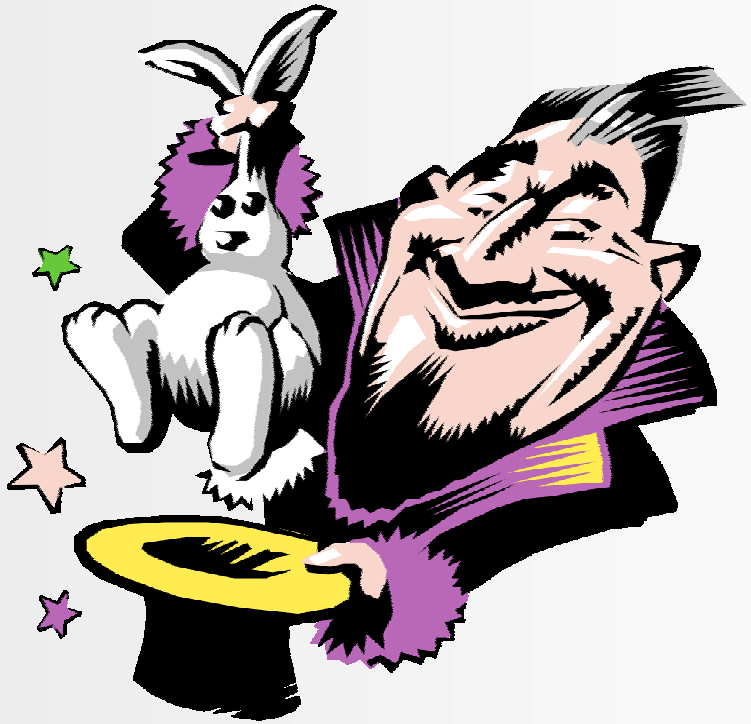
Pharmacovigilance tools



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Pharmacovigilance tools

- **Well-planned use of best available techniques to obtain and analyse information in the post-marketing phase is crucial. => case definition**
- **The observation and monitoring of the patient should contribute as much information as possible to support the Pharmacovigilance assessment at any time. => consumer reports, enhanced reporting**
- **Detailed knowledge of the pathophysiology of the disease and the pharmacology of the drug gained from the preauthorisation is essential for the causality assessment. => training and education of doctors**
- **Non-clinical pharmacology studies may are of special importance for assessment of ADRs => juvenile animal studies, pathomechanism**

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Pharmacovigilance tools

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Pharmacovigilance tools

- **case definition**
  - **data collection**
  - **data analysis**
  - **data presentation, assessment**
- **enhanced reporting**
  - **intensified monitoring at bed-side**
  - **Biomarker, surrogate markers**
- **pathomechanism**
  - **in vitro studies**
  - **animal studies/ juvenile animal toxicology studies**

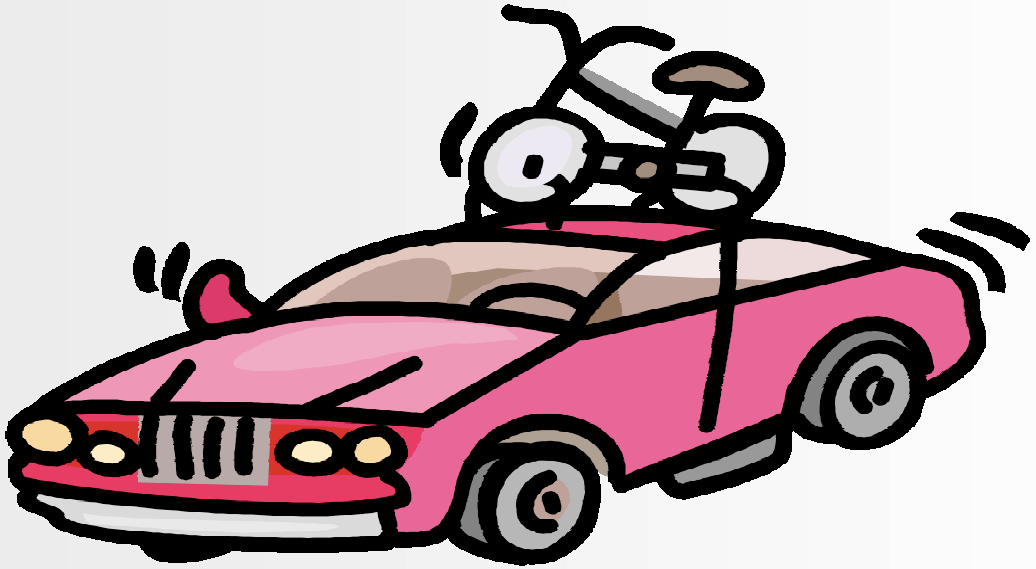
Aspects of Pharmacovigilance in Neonates

Pharmacovigilance tools

- **case definition**
  - **data collection => monitoring, clinical documentation**
  - **data analysis => normal values, scoring system**
  - **data presentation, assessment => publication, training**
- **enhanced reporting**
  - **intensified monitoring at bed-side => human resources**
  - **Biomarker, surrogate markers => appropriateness**
- **pathomechanism**
  - **in vitro studies => supporting non profitable research**
  - **animal studies/ juvenile animal toxicology studies**

Bewertung von Impfreaktionen

Present situation in Pharmacovigilance



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Present situation in Pharmacovigilance

- **Case reports of adverse drug reactions are particularly useful to detect potential associations between specific medicines and adverse events.**
- **The assessment of causality is more difficult when**
  1. there is a longer time lag between drug use and AE
  2. there is input on secondary effects like maturation
- **To establish a causal association, further research is necessary using cohort, case-control studies or randomized trials**
- **Randomized trials may be preferred from a methodological point, but are not always useful and practical in rare disease.**
- **Defining age-, gender- and calendar period specific risks from population-based disease registries for comparison.**

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Present situation in Pharmacovigilance

Patient registries - treatment registries

- important information on the natural course of disease
- help in the assessment of effectiveness and safety
- serve as a source for historical controls
- should meet high data quality standards
- not available in every EU-member state (data protection)

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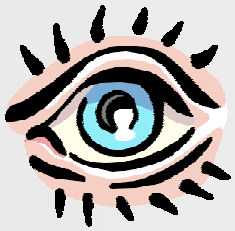
Further development



Pharmacovigilance

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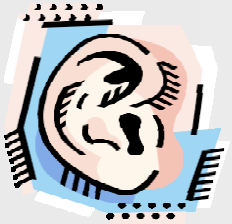
Further development

Risk Communication

Identified and potential Risks



Enhanced reporting and education

Surveillance and controlled trials

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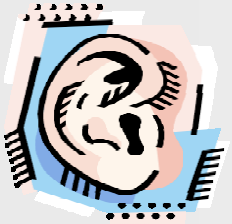
Further development

Risk Communication

- Rapid-Alert-System (NUI), DHCP,
- Warning SPC, PSUR

Identified and potential Risks



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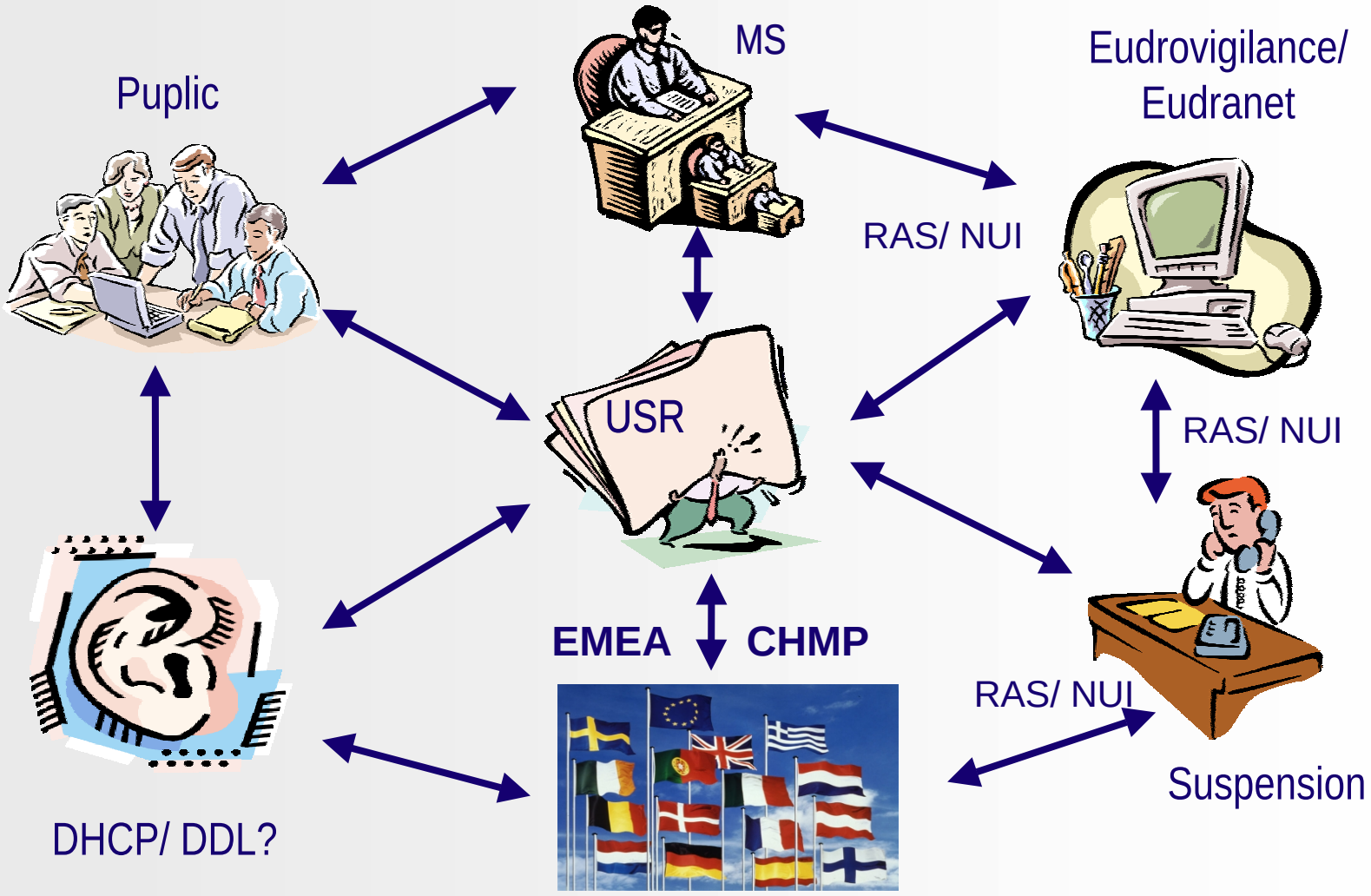

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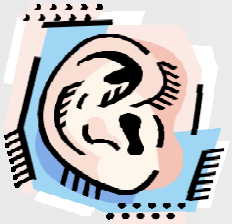
Identified and potential Risks

- registries, signal detection, in vitro studies
- research in pharmacovigilance



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Identified and potential risks

- **The incidence of adverse drug reactions in Off-label drug use is significantly associated with adverse drug reactions**
- **particularly when the drug was due to an indication different than that defined in the Summary Product Characteristics.**
- **Support of non-profitable research and research conducted by learned societies**
- **Post natal data collection to be linked with long-term follow up regarding late onset ADRs like growth, maturation (mentally and physically)**

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Further development

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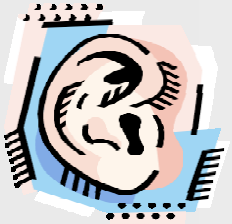

Enhanced reporting and education

- consumer (parents) reports
- simplified reporting via web-tool

Surveillance and controlled trials

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Enhanced reporting and Education

- **The mechanisms for detecting new safety signals like spontaneous reporting systems have to include the consumer (=> parents).**
- **The marketing authorisation holder and the regulatory authorities have to take appropriate measures to provide sufficient educational information (readability of SPC)**
- **Proactive approach is needed like: specialist networks, clinical pharmacologist in Paediatrics, disease and treatment databases and active surveillance and clinical trials networks (national and international)**

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Further development

Risk Communication

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Surveillance and controlled trials

- **Signal detection tools, Epidemiological studies**
- **Post-marketing safety studies/ surveilliance**

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Surveillance and controlled trials

- **Signal detection tools**

  Searching case report in a databases with the Proportional Reporting Ratio with an appropriate stratification of data in the data warehouse which needs to be established

- **Epidemiological studies using patient database**

  Provides information regarding the natural incidence of a specific event in the general population

- **Post-Marketing safety surveillance**

  Ideally estimates of the incidence of adverse reactions in the target population and provides a causal relationship between drug and adverse event and risk factors predisposing to specific adverse events.

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Thank you for your attention!