3rd DIA paediatric Forum
Clinical Development: Paediatric Risk Management
and Pharmacovigilance

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Paediatric Risk Management and Pharmacovigilance

Points to consider

- Legislation
- Guideline
- RMP Safety specification
- Pharmacovigilance aspects
- Present situation

3rd DIA Paediatric Form, London, 2009, Dirk Mentzer

• Regulation (EC) No 726/2004 of March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency


• Directive 2001/20/EC of April 2001 “Clinical trial directive”.
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Guidelines (ICH, CHMP)

• ICH Guideline E2E on Pharmacovigilance Planning

• Guideline on Pharmacovigilance in Paediatric population

• Guideline on Risk Management Plan and Pharmacovigilance Plan

• Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11)
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• Efficacy data (design, main parameters, estimated sample size, comparators (placebo versus standard of care)
• Safety data (long term / short term)
  - discuss potential risks by age group
  - discuss risk management plan, e.g. proposed pharmacovigilance measures including risk minimisation
• Post marketing experience and off-label experience
• Proposed studies post-authorisation
• Data and Safety monitoring
• Populations not Studied in the Pre-Approval Phase
  The Specification should discuss which populations have not been
  studied or have only been studied to a limited degree in the pre-
  approval phase. The implications of this with respect to predicting
  the safety of the product in the marketplace should be explicitly
discussed.
• Safety specification
• Potential Risks that require further investigation
• Targeted clinical investigation
• Stimulated reporting ADR reporting on a pre-defined method
• Active surveillance (Drug event monitoring, Registries)
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Pharmacovigilance aspects

- Clinical studies
- PMSS, Pharmaco-epidemiological studies
- Spontaneous reports
Challenge of Pharmacovigilance Planning

- Multifactorial Pharmacovigilance
- small numbers to be treated
- Indication and dosage
- appropriate formulation
- Organ impairment
Pharmacovigilance aspects

• 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, research

• pathomechanism
  - in vitro studies => supporting non profitable research
  - juvenile animal toxicology studies => defining animal model
# Paediatric Risk Management and Pharmacovigilance

## Pharmacovigilance aspects

<table>
<thead>
<tr>
<th>Method</th>
<th>Frequency of ADR</th>
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<tbody>
<tr>
<td>(-) without relevance</td>
<td>&gt; 1/10 - 1/1000</td>
</tr>
<tr>
<td>(+) possible supportive</td>
<td>1/1000 - 1/5000</td>
</tr>
<tr>
<td>(++) supportive</td>
<td>1/5000 - 1/10000</td>
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<tr>
<td></td>
<td>1/10000 - 1/50000</td>
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<td>&lt; 1/50000</td>
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| Spontaneous reports                        | +                |
| Intensives Monitoring                      | ++               |
| Prescription Event Monitoring              | ++               |
| Case-controll- Studies                     | ++               |
| PMS Studies                                | ++               |
| Large Data Resources (+record linkage)     | ++               |
| Clinical trials                            | ++               |

Methodes for detection of ADR incidence, Meyboom, Drug safety 1997
Pharmacovigilance aspects

• Signal detection tools
  Searching case report in databases with the Proportional Reporting Ratio (PRR) with an appropriate stratification of data in a data warehouse - needs to be tested and established

• Epidemiological studies using patient database
  Provides information regarding the natural incidence of a specific event in the general population - availability of data?

• 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. - possible number of patients included
• Required, if identified or potential risks need further minimisation activities. - PIP opinion/ waiver /deferral

• Listing safety concerns for which risk minimisation activities are needed - adult experience

• potential medication errors, education of caregivers - appropriate formulation

• Monitoring of the safety concerns and the proposed minimisation activities and rational for the proposed activities - post marketing safety surveillance, registries

• Evaluation of the effectiveness and milestones for evaluation and reporting - PIP compliance
Conclusion

- Case definitions for adverse reactions in children
- Indicator Symptoms for adverse reaction (pathophysiological understanding) to be specified in the EU-RMP
- Responsibility for long-term follow up (methods)
- Registries, huge linked databases for aggregation of knowledge
- More science, interdisciplinary network of scientists involving paediatric pharmacovigilance centres
- Development of treatment guidelines in collaboration with experts, proving relevance for the EU-RMP
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Thank you for your attention