BfArM
Bundesinstitut für Arzneimittel
und Medizinprodukte

# Ethical Considerations for Clinical Trials performed in Children

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DAKJ-Workshop

Berlin, 01.12.2006

# Regulatory framework specifically addressing paediatric medicines

Guideline ICH E11

Guideline on PhV for paediatric medicines

Article 4 of the Clinical Trials Directive (Directive 2001/20/EC) ✓

↓

Recommendations regarding ethical considerations for clinical trials performed in children ✗

Paediatric Regulation (Regulation EC xxx/2006) (✓)

↓

Commission guideline regarding format and content of paediatric investigation plans ✗

Reflection paper on formulation of choice

Guideline on clinical trials in small populations

Concept papers regarding medicines for neonatal use

Lists of therapeutic needs for paediatric medicines

Guideline on PK in the development of paediatric medicines

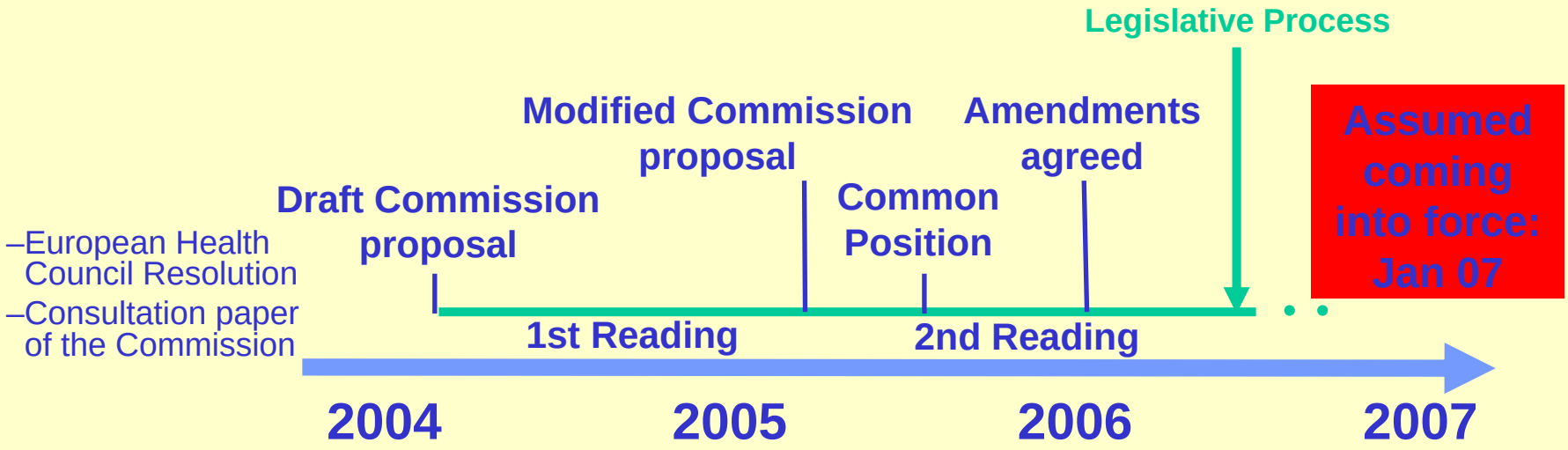
Note: The list of additional documents (like guidelines) mentioned in this overview is not complete.

# Topics to be addressed

1. The evolving regulatory framework addressing development of paediatric medicines
   - Paediatric Regulation
   - Guideline re Paediatric Investigation Plans
   - Clinical Trials Directive
   - National transposition in Germany
2. Draft recommendations re ethical considerations for clinical trials performed in children
   - Objectives and background
   - Content
   - Specific aspects
3. Conclusions

# The EU Paediatric Regulation
## *Objectives and Timelines*

- To facilitate the **development and accessibility** of medicinal products for use in the paediatric population.
- To ensure that medicinal products used to treat the paediatric population are subject to **ethical research of high quality** and are **appropriately authorised** for use in the paediatric population.
- To **improve the information available** on the use of medicinal products in the various paediatric populations.



# The Paediatric Regulation
# *Key elements*

**Requirements:**

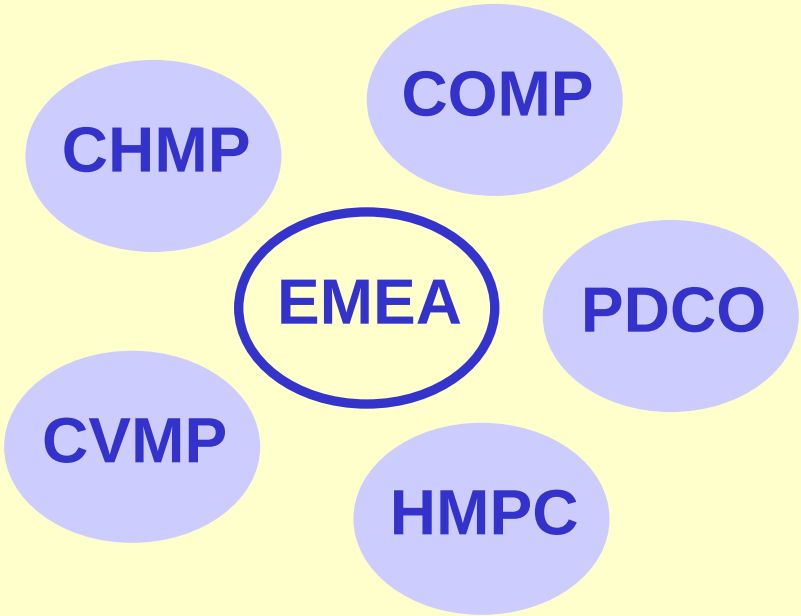
- Agreement of a Paediatric Investigation Plan (PIP)
- Submission of paediatric data with the MAA for all new medicinal products unless waiver or deferral is granted
- Requirements for line extensions

**Incentives:**

- 6-month SPC extension
- Paediatric Use Marketing Authorisation (PUMA)
- Additional market exclusivity for orphan medicinal products
- Community/MS incentives and Community funds

**Others:** Scientific advice free of charge, symbol for identification of products for paediatric use, additional pharmacovigilance requirements, requirements wrt placing on the market and discontinuation, use of the EudraCT database, requirements regarding existing paediatric data, inventory of therapeutic needs, creation of an European network of excellence, etc.

# The Paediatric Committee (PDCO)




**Main task:**

- Assessment and formulation of opinions wrt Paediatric Investigation Plans and waivers/deferrals

**Others:**

- Advice on surveys re existing paediatric use
- Support of the EMEA re the network of paediatric experts
- Providing advice (on request)
- Establishment of an inventory of paediatric needs
- etc

**Consideration of whether proposed studies can be expected to be of significant therapeutic benefit and/or fulfil a therapeutic need of the paediatric population!**

# Paediatric Investigation Plan
## *Content and timelines*

| | |
|---|---|
| Definition: | R&D programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population. |
| Content: | – Timing and the measures proposed to assess Q/S/E in all subsets of the paediatric population that may be concerned.<br>– In addition, any measures to adapt the formulation of the medicinal product for its use in the paediatric population. |
| Time of submission: | Not later than upon completion of the human pharmacokinetic studies in adults. |

# Commission guideline

**Key document for the procedures related to the PIP*:**

→ Detailed arrangements concerning format and content for
- agreement
- modification

of PIPs and requests for waivers/deferrals

→ Operation of the compliance check

→ In addition, guidance on
- significant therapeutic benefit
- fulfilling a therapeutic need
- significant studies

* Content as outlined in the EC/EMEA document re Implementation Priorities (September 2006)

# Directive 2001/20/EC

*Article 4*

**Clinical trials on minors**

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

# Legal requirements in Germany I
# *Studies in paediatric subjects*

## Article 40 Section 4 German Medicines Act

⇨General requirements:

1. Product must be for diagnosis or prophylaxis of paediatric diseases and according to current scientific knowledge the use of product needs to be indicated to diagnose or prevent the disease in the paediatric study participant.
2. Paediatric studies only if studies in adults or alternative methods are not expected to generate sufficient data.
3. Requirement to obtain informed consent from the legal representative as well as to inform the paediatric individual considering its capacity of understanding and to respect its wish.
4. Principle of minimal risk/minimal burden with the need to define the level of burden and risk in the study protocol including monitoring.
5. No incentives allowed expect compensation.

# Legal requirements in Germany II
# *Studies in paediatric patients*

## Article 41 Section 2 German Medicines Act

⇨ Special requirements for studies in paediatric patients:

- The use of the medicinal product must be considered appropriate to be life-saving, restore health or relieve disease for the participating patient according to the scientific knowledge.

OR

- Benefit for the group must be assumed.
- Research to confirm data from other trials or other research methods must be ultimately necessary.
- Research must be related to the clinical condition of the paediatric study participant.
- Principle of minimal risk/minimal burden for the individual needs to be maintained: minimal risk = minimal and transient impairment if any; minimal burden: minimal and transient discomfort if any

# Legal requirements in Germany III
# *CT assessment of paediatric studies*

## Article 42 German Medicines Act

⇨Grounds for rejection

| Ethics Committee | BfArM |
|---|---|
| -Documentation including study protocol, /…/, selection of study participants, not adequate to assess efficacy and safety acc. to scientific knowledge<br>-**Requirements of Article 40 Section 4 and Article 41 not fulfilled** | -Documentation including study protocol, /…/, not adequate to assess efficacy and safety acc. to scientific knowledge |

# Draft Recommendations on ethical considerations

**ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS PERFORMED IN CHILDREN**

**Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use**

| | |
|---|---|
| DRAFT AGREED BY AD HOC WORKING GROU | 12 September 2006 |
| RELEASE FOR CONSULTATION | 4 October 2006 |
| END OF CONSULTATION (DEADLINE FOR COMMEN | 31 January 2007 |
| AGREED BY WORKING GROUP | |

- Prepared by the ad-hoc group for guidelines related to Directive 2001/20
- Released for consultation on the EC website

# Background on the development of the recommendations

Rationale:

⇒ Protection of the children involved in clinical trials

⇒ Facilitation of clinical trials across the EU acknowledging the competence of MS wrt CT approval

**Need to conduct studies versus best possible protection**

- Specific protection to be defined for research performed in children, at all stages and ages
- If possible studies should be done in less vulnerable patients (i.e. adults); if research in children is necessary then the less vulnerable (i.e. older ones) should be considered first

# Background on the development of the recommendations

Scope:

- ⇒ Guidance on ethical aspects of the performance of clinical trials within the scope of Directive 2001/20
- ⇒ Intended for sponsors of clinical trials, Ethics Committees as well as investigators of paediatric trials
- ⇒ To be read in conjunction with the appropriate legal texts and guidelines

<u>Underlying Ethical principles:</u>

- Declaration of Helsinki, UN Convention of the Right of the Child, etc. (see ICH E6)
- Belmont principles (beneficence, justice, and respect to persons)

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# Annex – Divergence within the EU

| MS | AT | BE | BG | CY | CZ | DK | ES | FI | FR | GE | GR | HU | IS | IE | IT | LV | LT | LU | MA | NO | PL | PT | RO | SL | SP | SW | NL | UK | CH |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Law on consent | | | | | Y | Y | Y | Y | Y | Y | | Y | | | | Y | Y | | Y | | Y | | | | Y | Y | | Y | |
| Legal Repres. legal Definition | | | | | N | Y | Y | Y | Y | Y | | Y | | | | Y | Y | | Y | | Y | | | | Y | N | | Y | |
| Guidelines on consent | | | | | Y | Y | Y | Y | Y | Y | | Y | | | | N | Y | | Y | | N | | | | N | Y | | Y | |
| Guideline on Legal Repres. | | | | | Y | Y | - | Y | Y | N | | Y | | | | Y | Y | | N | | N | | | | N | N | | Y | |
| One parent consent | | | | | Y | N | Y | Y[9] | Y[10] | Y | | Y | | | | Y | N | | - | | Y | | | | Y | N | | Y | |
| 2 parents consents | | | | | - | Y | - | Y | Y | N | | N | | | | N | Y | | Y | | - Y? | | | | - | Y | | N | |
| Disagreement between parents GL | | | | | - | N | N | Y | N | N | | N | | | | Y | N | | Y court | | Y court | | | | Y | Y | | Court | |
| Law Child assent | | | | | Y | Y | Y | Y | Y | Y | | Y | | | | Y | N | | Y | | Y | | | | Y | Y | | Y | |
| GL child assent | | | | | N | Y | N | Y | Y | N | | Y | | | | N | Y | | Y | | N | | | | - | Y | | Y | |
| Assent required | | | | | Y | Y | Y | Y | Y | Y | | Y | | | | Y | Y | | N | | Y | | | | Y | Y | | Y | |
| From age | | | | | NS | NS | 7 | 15 | NS | NS | | NS | | | | 7 | NS | | NS | | 16 | | | | 12 | NS | | NS | |

# Informed consent I

⇒ Definition according to Directive 2001/20

⇒ Parents / legal representatives are entitled to give informed consent (reference to definitions in national law)

⇒ Written informed consent may also be required from adolescents aged 16 to 18

- Informed consent must be sought prior to enrolling into a trial
- Sufficient time and necessary information needed
- Information to be provided to each parent / legal representative by experienced investigator
- No undue pressure when seeking informed consent (no financial inducement, information about possibility to revoke and the fact that treatment is not prejudiced by withdrawal, consent to be sought before assent)

# Informed consent II

- ⇒ Cultural mediator where appropriate (language, social habits, culture, traditions, religion, ethnic problems)
- ⇒ Consent / assent to be sought at the beginning of the trial and during its conduct (ongoing dialogue between children, parents and investigators)
  Note: Informed consent to be sought in case of change of legal representative
- ⇒ **Informed consent in emergency situations** (not addressed in Directive 2001/20):
  - Inclusion without consent is a major concern
  - It may be unethical not to conduct research in these situations
  - Consent to be sought acc. to national law – ECs to assess
  - Retrospective consent (and thereafter assent) to be sought as soon as possible

# Assent from children I

- ⇒ **Definition: The child's will to participate in a trial**
- ⇒ Assent is not specifically addressed in Directive 2001/20 (i.e. no legal requirement) – it is nevertheless recommended to obtain assent (age permitting)
  - If no assent is sought then this should be recorded in the informed content form
  - Assent is not sufficient for inclusion into a trial
  - Specific information and forms should be used appropriate to age, psychological and intellectual maturity
  - Assent should also be obtained during the trial and duly considered (unless detrimental to his/her health)
  - Information about the possibility to withdraw
- ⇒ Differences between opinions between child and his/her legal representative should be respected

# Assent from children II

Neonates (term and preterm), infants and pre-school children:

- Not possible to obtain assent; age-appropriate information may be needed if the child has capacity of understanding

Children of school age:

- Need to obtain assent, preferably in writing, and to keep track of it
- Specific information needed to explain benefit and risks w/o conflicting or abstract information

Adolescents:

- Depending on the individual capacity consent might be possible and this should be respected
- Protection of confidentiality is a potential issue hence assent is very important (discretion, professional secrecy)
- Emancipated adolescents can provide additional informed consent
- Special situation when adolescents become parent

# Ethics committee I

- ⇒ Paediatric expertise needed for providing an opinion on paediatric clinical trials (acc. to Directive 2001/20) – permanent member or ad-hoc expert
- ⇒ Needed for initial protocol as well as for any subsequent significant amendments
- ⇒ **Definition:** Education and experience on the various aspects of child development, ethics and psychosocial aspects
  - (1) Physicians with paediatric qualification
  - (2) Paediatric ethicists
  - (3) Qualified paediatric nurses or psychologists, etc.

  plus demonstration of some years experience in paediatric care and direct experience of clinical trials
- ⇒ Two or more experts may combine the expertise needed
- ⇒ Expertise should be recorded and documented by the EC

# Ethics committee II

**When giving an opinion it needs to be checked that**

⇒ **The protocol is adequate wrt paediatric protection;**

⇒ **The research to be scientifically sound (liaison with CA).**

- Protection of children is ensured, paediatric expertise at trial site
- Justification for inclusion of children and choice of age groups
- Appropriate non-clinical data is available
- Exhaustive review of available evidence (no replication!)
- Results supposed to be interpretable (monitoring, audit, QA)
- Use of age appropriate formulations
- Independent DSMB identified in the protocol (otherwise justified)
- Provisions for systematic independent publication
- Provision of medicinal product after the trial described in the protocol
- Permanent monitoring of B:R balance (CA and EC!)
- No treatments known to be inferior to existing treatments (placebo!)

# Paediatric clinical trial design

- ⇒ Depending on objectives and scientific questions
- ⇒ Consultation of older children or adolescents may be appropriate
- ⇒ Avoidance of bias (open a/o uncontrolled trials to be avoided)
  - Open trials: at least blinding of assessments
  - Uncontrolled trials: to be avoided for efficacy, of limited use for safety (unless prospectively used for follow-ups and cohorts)
  - Alternative designs should be justified and ideally agreed with CAs
  - Size should be as small as possible to demonstrate efficacy with sufficient statistical power
- ⇒ Use of placebo:
  - More restrictive than in adults although sometimes needed for scientific reasons (then use on top of SOC)
  - Measures to minimise exposure and to avoid irreversible harm
  - Rescue treatment a/o escape procedures should be set-up
- ⇒ Active comparator may be appropriate even if unlicensed but if it represents evidence-based SOC

# Pain, distress, and fear minimisation

⇒ Pain to be prevented as much as possible, otherwise effective treatment
- Assessment of intensity as well as monitoring (validated scales)
- Effective treatment (patient-controlled analgesia)
- Painful procedures to be minimised, non-invasive procedures preferred; PopPK approaches to be considered
- Appropriate information of parents / legal representatives

⇒ Facilities to be appropriate to childcare, personnel to be trained and supervised by experienced personnel, “familiar environment” (furniture, toys, activities, school attendance)

⇒ Fear to be prevented / minimised:
- Need for comfort and re-assurance
- Appropriate information needed
- Changes to be announced, no separation of the child from the parents or familiar persons whenever possible

# Level of risk I
## *Assessment and monitoring*

⇒ **Definition:** potential harm (real or theoretical) or potential consequence of an action; physical, psychological, or social; immediate or delayed

⇒ Assessment wrt probability, magnitude, and duration

- Risk of the product or the control, risk of withholding treatment, risk of the disease
- Harm thorough invasiveness, intrusiveness of research, severity / seriousness; reversibility of AEs, preventability
- Timing of paediatric studies (adult data, preclinical data)
- Lack of an age-appropriate formulation
- Pre-symptomatic diagnosis
- Violation of privacy
- In case of emerging issues potential conflict between child's interest and research interest – child's interest always prevails!
- Possibility of external risks

# Level of risk II
## *Assessment and monitoring*

- ⇒ Risk assessment is difficult as probability is unknown – elements to influence risk to be identified in the protocol
- ⇒ Identified risks to be described w/ measures to prevent, minimise and monitor these risks
  - Reference to legislation in France, the UK and the US
- ⇒ DSMB is recommended to perform monitoring of risk assessment (stopping rules to be defined)
- ⇒ Risks should be identified and assessed in the ASR
  - Specific analysis of patient's safety in paediatric trials
  - Update on B:R assessment for the paediatric population

# Measures of Benefit

- ⇒ **Benefit (direct or indirect) should be expected in any paediatric trial!**
- ⇒ Benefit = progress in treatment, diagnosis / prevention: better or at least similar B:R balance, or contribution to patient care
  - Potential direct benefit of the children in the trial
  - Assessment wrt gender, ethnic group, cultural background
- ⇒ Direct benefit for the group (reference to the European Convention as well as Directive 2001/20)
  - Benefit to other persons in the same age category or afflicted with the same disease / disorder or having the same condition
  - Minimal risk / minimal burden for the individual concerned

# Other topics

**Assays / Blood sampling**
- Age / BW to be considered, trained staff, anaesthetic procedures as appropriate
- In neonates NMT 3% of total blood volume per trial (monitoring!)
- Timing carefully to be considered

**Special populations**
- Neonates: Complexity (interactions!); potential long-term effects
- Healthy children : Very restrictive, only for special trials like prevention trials or vaccine trials

**Unnecessary replication of trials**
- Publications
- Transparency (measures in the Paediatric Regulation)

**Insurance**
- Potential issues, in particular for studies in neonates (EC!)

**Ethical violation, non-compliance with GCP**
- Special role of EC and CA

# Exchange and discussion is needed!
## *Round Table Discussion of PAED-Net*

**In the light of the evolving EU Paediatric Regulation, representatives of the NCAs (BfArM, PEI), the Ethics Committees, the industry associations and the paediatricians discussed on 29.09.2006 the following:**

- Definition of minimal burden/minimal risk
  - →PK studies should be possible
- Informed consent of minors
- Requirements regarding signatures from parents/legal representatives
- Inclusion/exclusion of girls
- Pharmacovigilance concept in Germany

# Exchange and discussion is needed!
## *Further examples*

**Workshop on Regulatory and Scientific Issues related to the investigation of Medicinal Products intended for Neonatal Use (11th October 2006)**

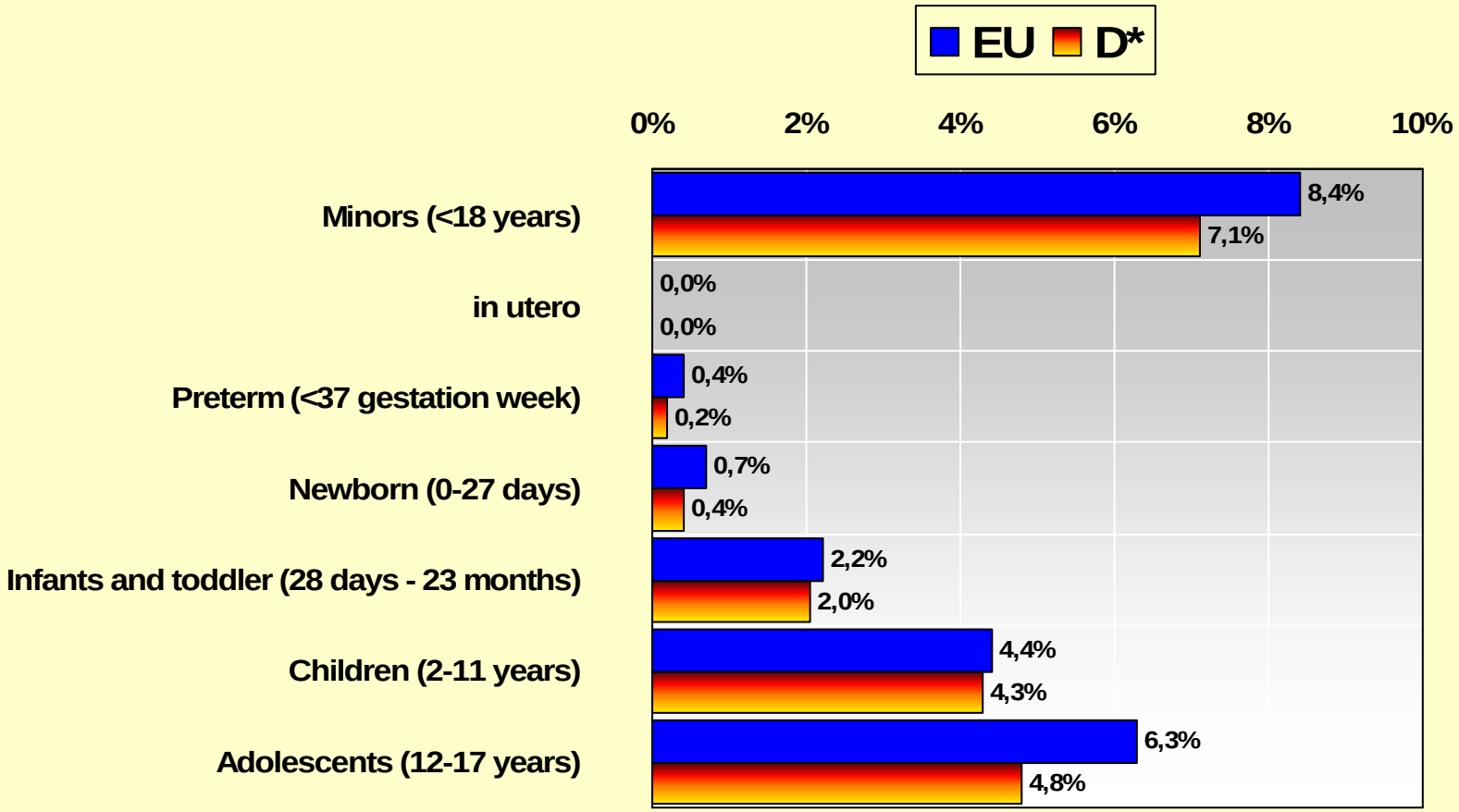
Participants from PEG, National Agencies, Academia, Industry, EMEA

**EFGCP Children's Medicines 2nd Annual Conference : "How can the EU Paediatric Regulation meet Expectations from the beginning?" (5th October 2006)**

Participants from Academia, EMEA, National Agencies, Industry, Patient Organisations, Paediatric Networks

# Statistics regarding paediatric trials

## *Period 01.09.2004 – 01.07.2006*




* BfArM and PEI

# Conclusions

- → Paediatric medicines are in the focus of the Regulatory environment and its further development
- → The Paediatric Regulation will enter into force at the beginning of 2007 resulting in an increase of studies being conducted in the paediatric population
- → There are differences between MS regarding aspects relevant for the ethical assessment of paediatric studies
- → **The evolving document on ethical considerations for clinical trials performed in children will be important piece in this framework**
  - ☞ Commenting from all stakeholders needed (email to entr-pharmaceuticals@ec.europa.eu)
- → These recommendations will be helpful for the protection of paediatric subjects in clinical trials as well as the facilitation of trials across the EU

# Thank you!