Belgian Federal Agency for Medicines and Health Products
(FAMHP)

European Union Regulatory Perspective

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Non-clinical Regulatory Framework

Regulation on 'Medicinal Products for Paediatric Use'
(EC) N° 1901/2006
Jan 2007

Guideline on the 'Need for Non-clinical Testing inJuvenile Animals of Pharmaceuticals for Paediatric Indication'
(CHMP/SWP/169215/2005)
Aug 2008

Note for Guidance ICH Topic M 3 (R2)
(CPMP/ICH/286/95)
Dec 2009

Paediatric Regulation (EC) N° 1901/2006

One major pillar of the regulation: the Paediatric Investigation Plan.

•Basis for development and authorisation of a medicinal product for all paediatric population subsets.

•Obligation: for any new medicinal product under development, or for marketed product in case of new indication/ route/ formulation.

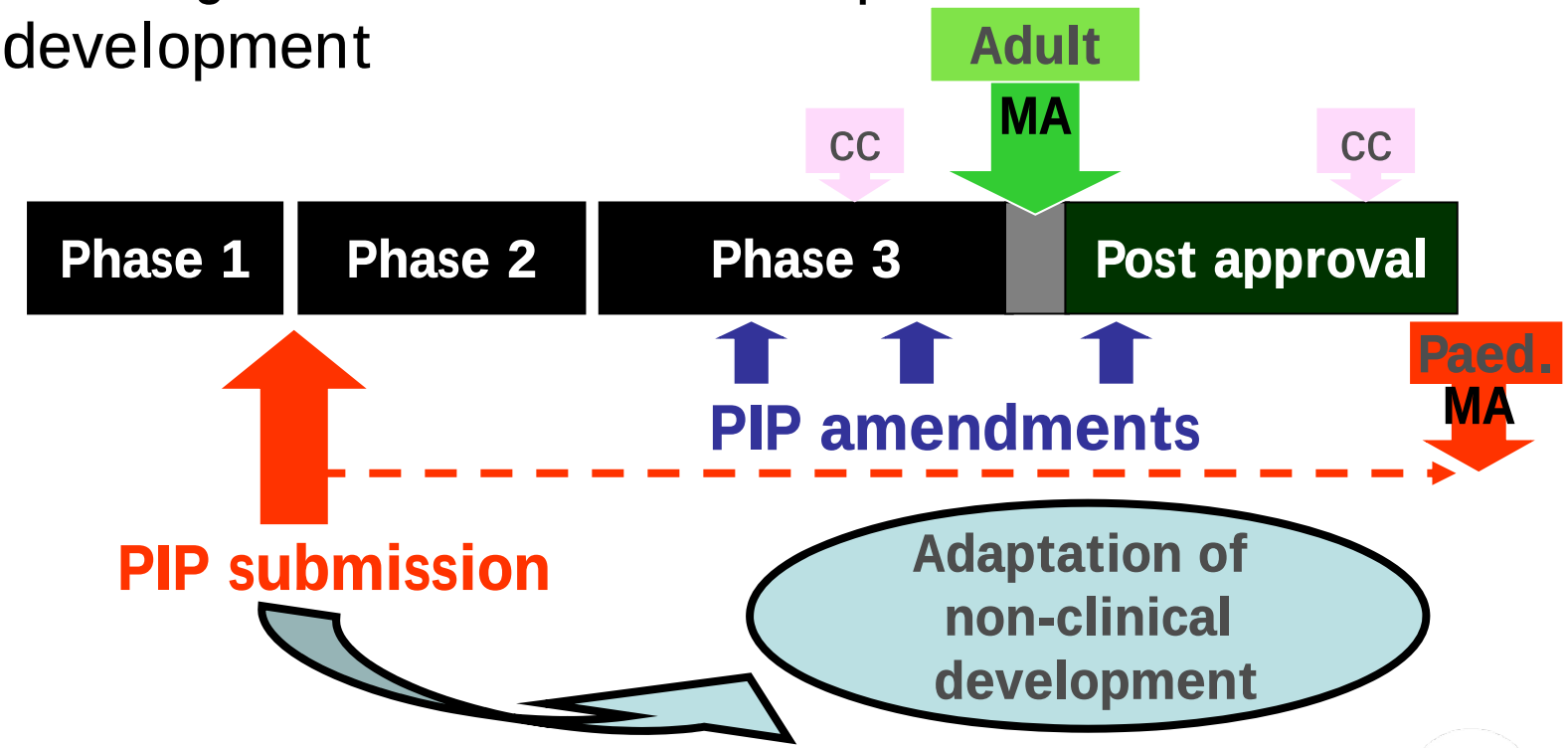
•Includes details of the timing and the measures proposed, to demonstrate:

		Strategies
•**Quality** •**Safety** •**Efficacy**	Marketing Authorisation Criteria	Quality: age adapted form. **Non-clinical: juvenile studies**? Clinical: studies and timelines

Paediatric Regulation (EC) N° 1901/2006

One major pillar of the regulation: the Paediatric Investigation Plan.

- Timing: for a new medicinal product under development



Paediatric Regulation (EC) N° 1901/2006

One major pillar of the regulation: the Paediatric Investigation Plan.

- To be agreed upon and/or amended by the **Paediatric Committee (PDCO - EMA)**

- Binding on company → compliance check
(but modifications possible, at the company's request)

Paediatric Committee

- **29 countries.**

- **1member + alternate per member state:**
  - **~ 80% physicians (~75% paediatricians)**
  - **~ 60% agency represent., 40% academics**

- **9 representatives from patients and prof. org.**

- **13 meetings per year (first: July 07)**

Paediatric Regulation (EC) N° 1901/2006

Non-clinical Working Group:

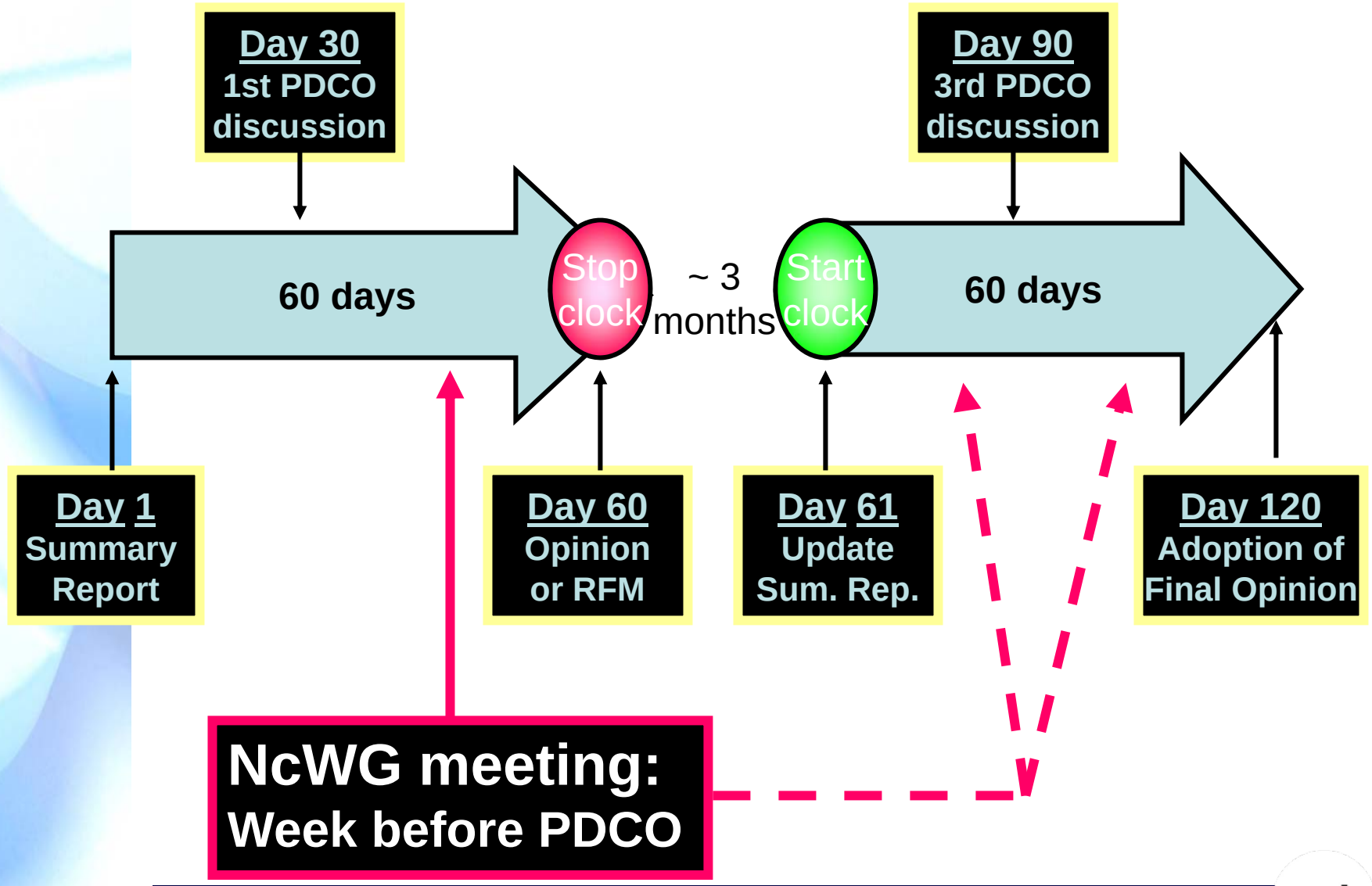
- The objectives of this working group are:
  - To ensure consistency
  - To share workload and experience
  - To provide guidance

- Composition:
  - 12 core members: agency nonclinical experts, including members from the SWP, and from the PDC0
  - Additional nonclinical experts on a case by case basis
  - EMEA coordinators

- Outcome: recommendation to the PDCO

- Meetings: once a month (first: Nov 2008)

Paediatric Regulation (EC) N° 1901/2006



Non-clinical Testing in Juvenile Animals (CHMP/SWP/169215/2005)

- **Juvenile animal studies should be considered:**
  - in case of findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials.
  - when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support pediatric studies.
- The **need for and design** of non-clinical studies in juvenile animals will vary depending on:
  - The clinical plan (paediatric population, dosing regimen…).
  - The data from previous adult human exposure and the data from previous animal studies including from compounds with similar safety profile or pharmacological activity.

Non-clinical Testing inJuvenile Animals (CHMP/SWP/169215/2005)

Study design:

- **Duration of dosing and age of animals at start**:

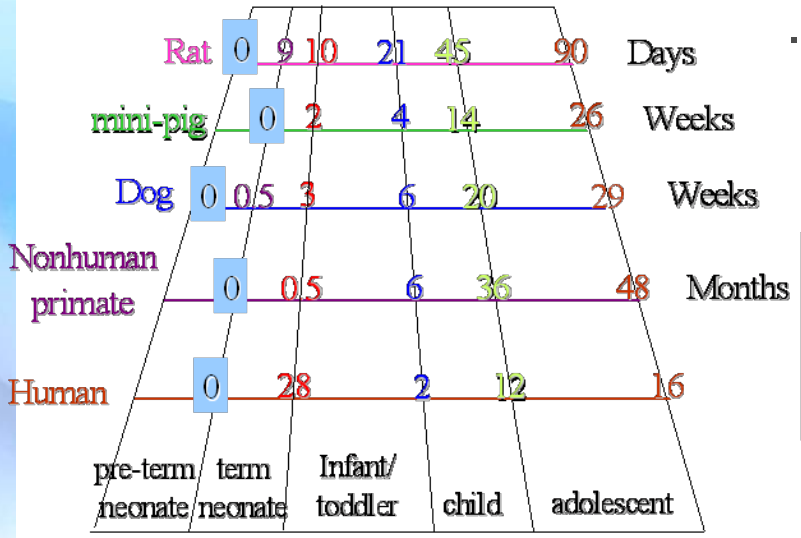
.Age of the target paed. population

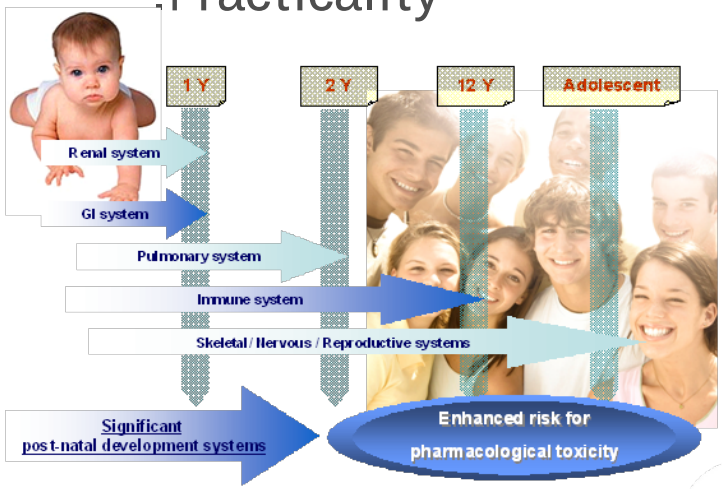
.Target organ/system

.Long term vs short term devlpt

.Reversibility

.Practicality





Non-clinical Testing inJuvenile Animals (CHMP/SWP/169215/2005)

Study design (cont'd):

- **Species:**
  - in general **one species**
  - appropriate for evaluating toxicity endpoints relevant for the intended pediatric population (PK;PD; Toxicology; feasibility)

- **Doses:** to detect increased sensitivity vs adult animals
  - **High-frank toxicity not desirable**
  - Low dose: clinical exposure

- **Endpoints:** to be determined on a case by case basis.

ICH Topic M 3 (R2) (CPMP/ICH/286/95)

Timing vs paediatric trials:

• Juvenile animal toxicity studies are not considered important for short-term PK studies (e.g., 1 to 3 doses) in paediatric populations.

• Juvenile animal toxicity studies should be considered before initiation of short-duration multiple-dose efficacy and safety paediatric trials.

•Juvenile animal toxicity studies should be completed before the initiation of the long-term clinical trials in pediatric population.

Paediatric Regulation (EC) N° 1901/2006

PIPs: Nonclinical Section

- Existing data (adult and juvenile if any):
  - At least repeated dose toxicity, safety pharmacology, and reproduction toxicity studies, genotoxicity testing…
  - Nc POC studies in adults.
  - Discuss the clinical relevance of these data in adult patients.
  - Existing juvenile data.

- Justify the non-clinical development strategy:
  - Justification of the juvenile toxicity study designs: species, age, duration of treatment. RF studies?
  - Justify why juvenile studies are not warranted.
  - Justify the potential extrapolation of adult POC data to children or propose studies to address efficacy in the paediatric population.
  - Specify which studies (including non juvenile studies) should be completed before dosing children.
  - Based upon actual or published nonclinical or clinical data.

Paediatric Regulation (EC) N° 1901/2006

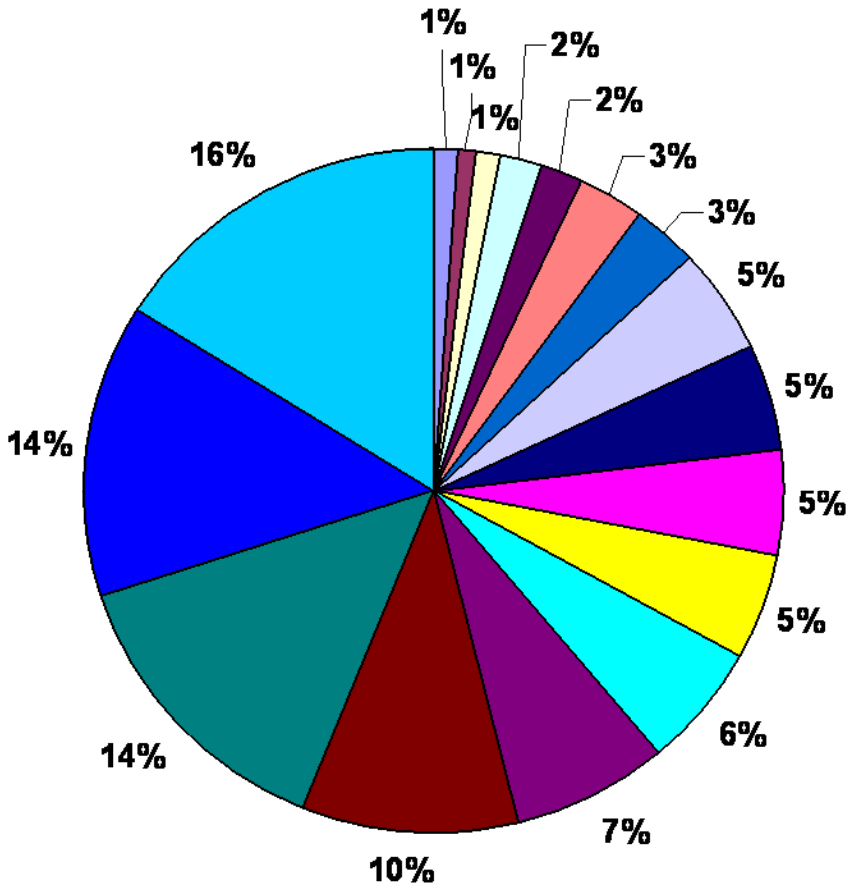
PIPs: Nonclinical Section

- **Requests for additional information on (most frequent cases):**

  - **Justification of the study design of juvenile studies: actual age (non rodents), study duration…**
  - **Timing of the studies vs the paediatric studies**
  - **Reproduction studies**
  - **Pharmacokinetics, metabolism when related to toxicity**
  - **Dependence potential**
  - **Potential carcinogenicity (when cause for concern)**
  - **Pharmacology in juvenile animals or in vitro paediatric tissues… (POC, extrapolation from adult data…)**

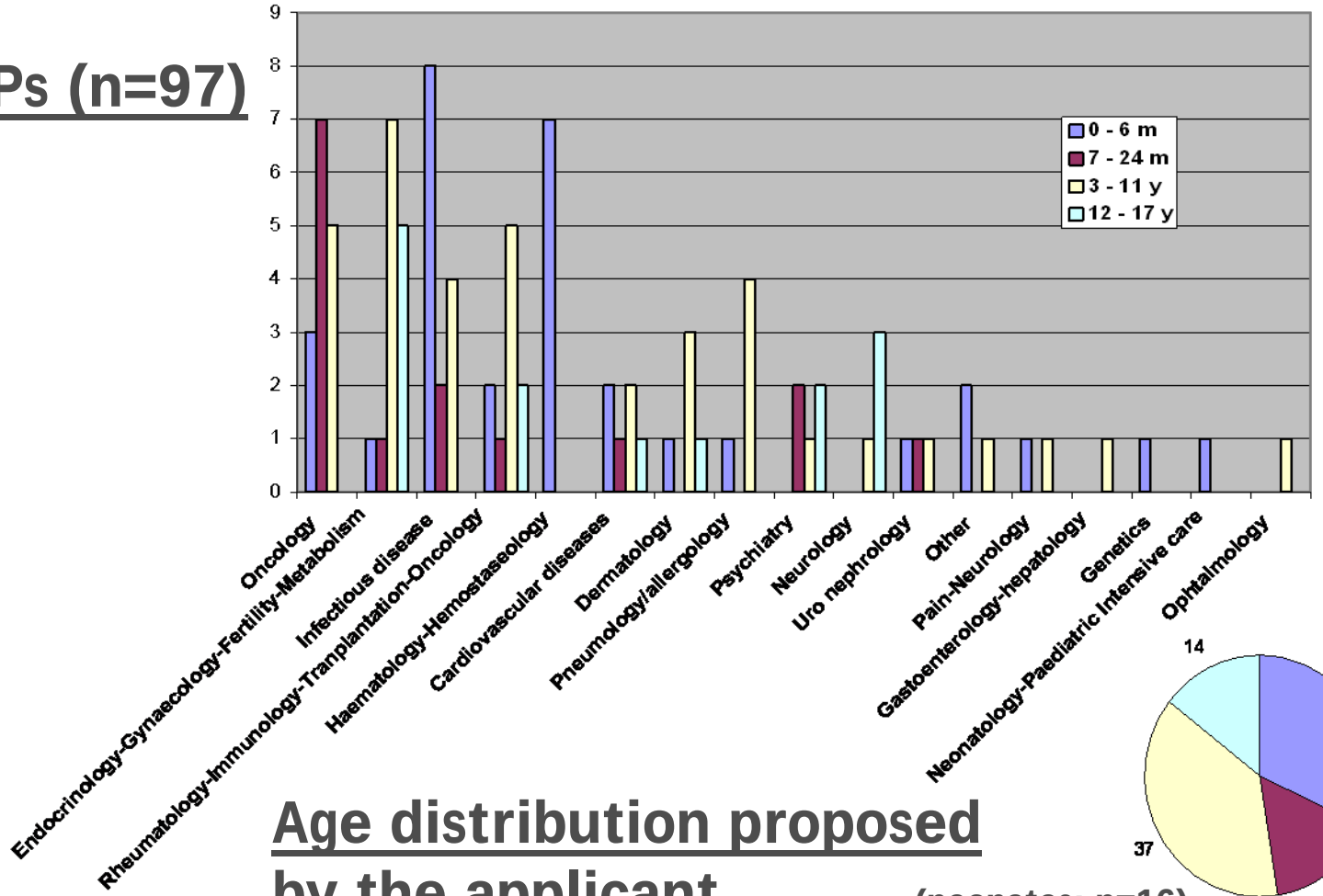
Non-clinical working group statistics (Nov 2008-Oct 2009)

Therapeutic fields (n=100)



Non-clinical working group statistics (Nov 2008-Oct 2009)

PIPs (n=97)

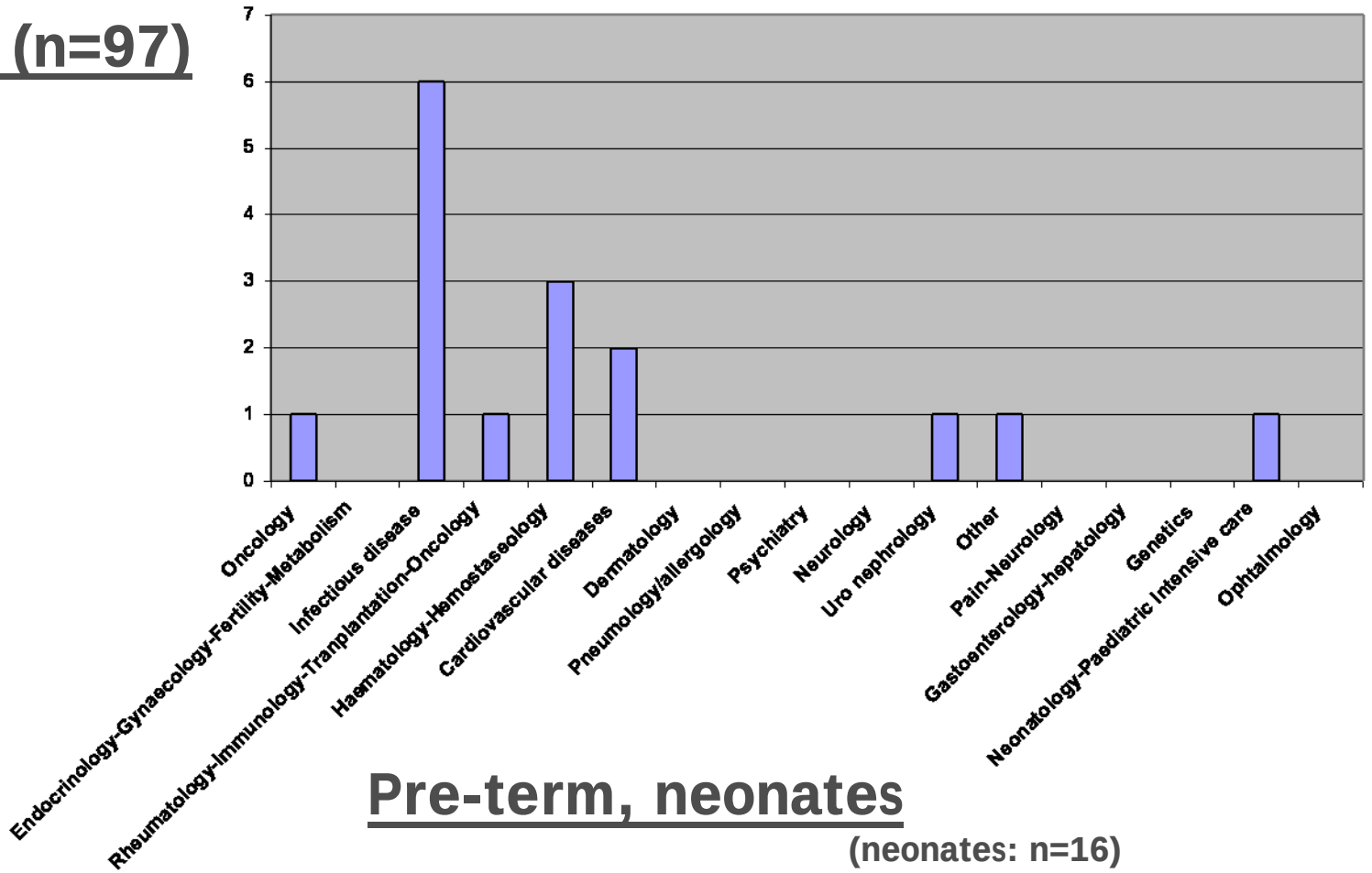


Age distribution proposed by the applicant

(neonates: n=16)

Non-clinical working group statistics (Nov 2008-Oct 2009)

PIPs (n=97)

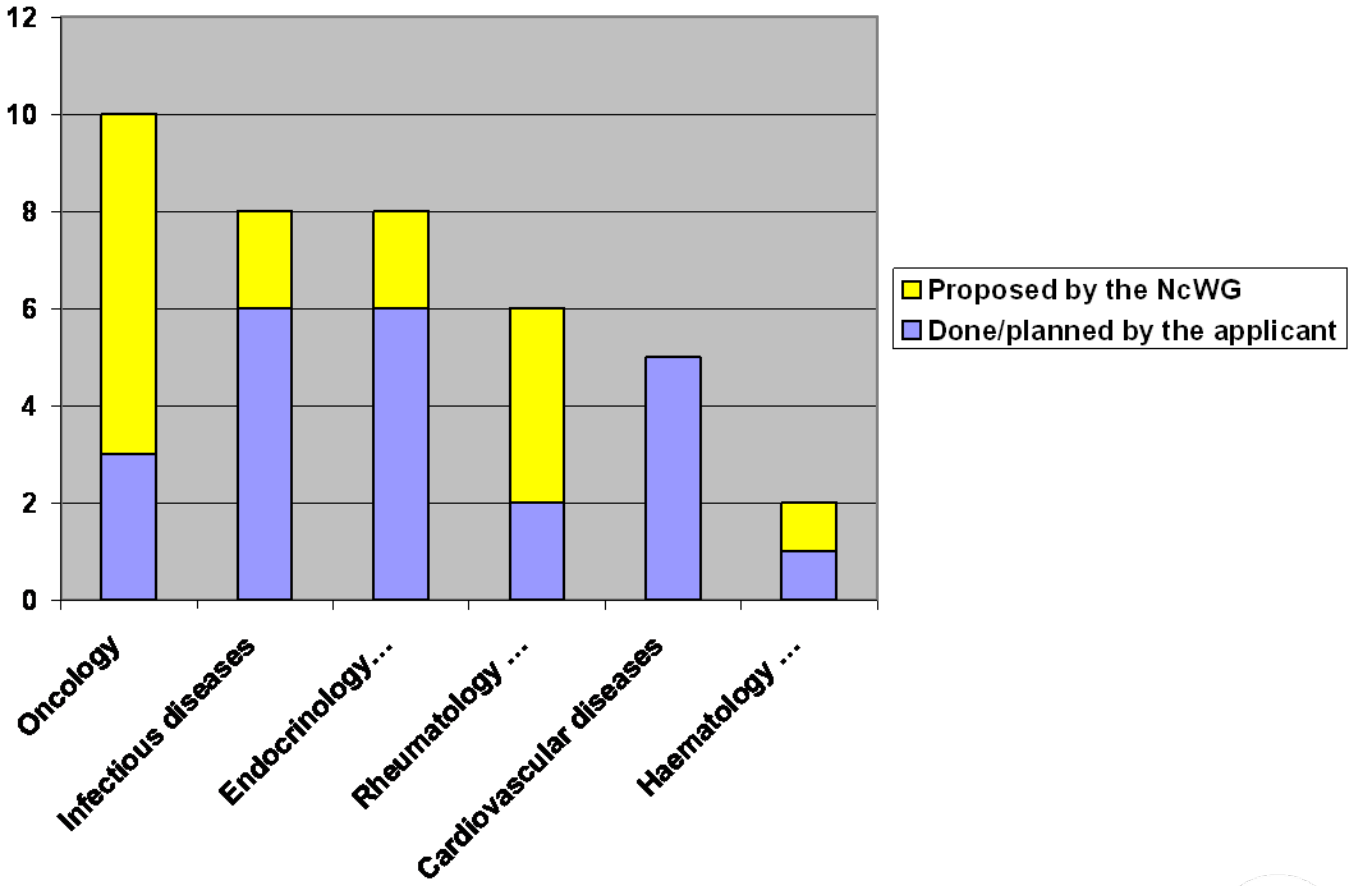


Pre-term, neonates

(neonates: n=16)

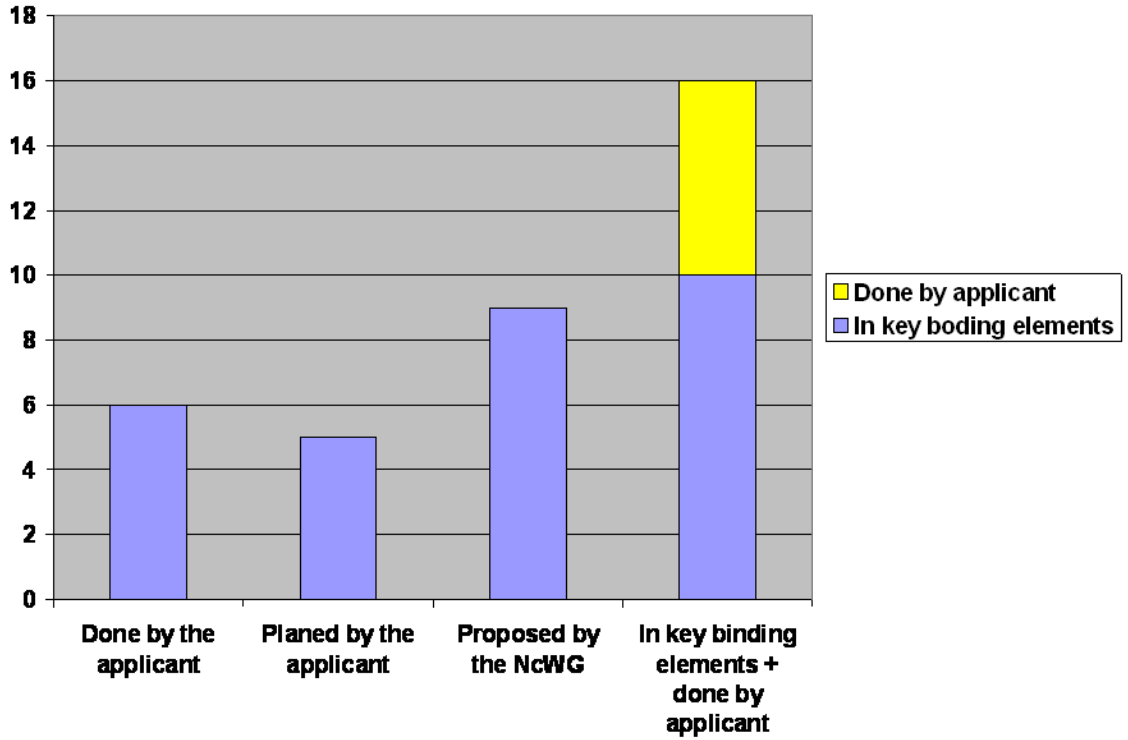
Non-clinical working group statistics (Nov 2008-Oct 2009)

PIPs with JAS: applicant vs NcWG



Non-clinical working group statistics (Nov 2008-Oct 2009)

Final opinion:PIPs with juvenile studies request (n=32)



Non-clinical working group statistics

Request for modifications: justification/concerns

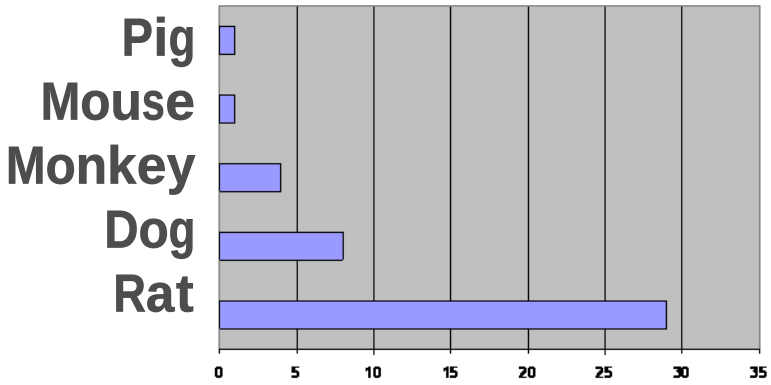
- Modification of the proposed studies (n=14)
  - Request for clarification of study design
  - Request / justification of endpoints
  - Study duration
  - Timing
  - Species selection
  - Route of administration

- Request for juvenile studies (n=25)
  - Change of clinical plan (age of the paediatric population)
  - Toxicity signals
  - Lack of information

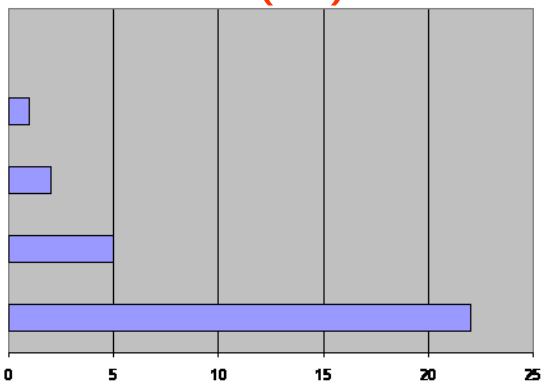
Non-clinical working group statistics

Species distribution:

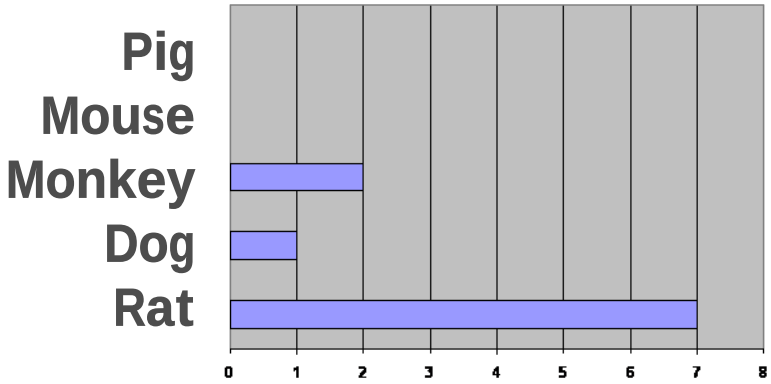
Applicant (43):



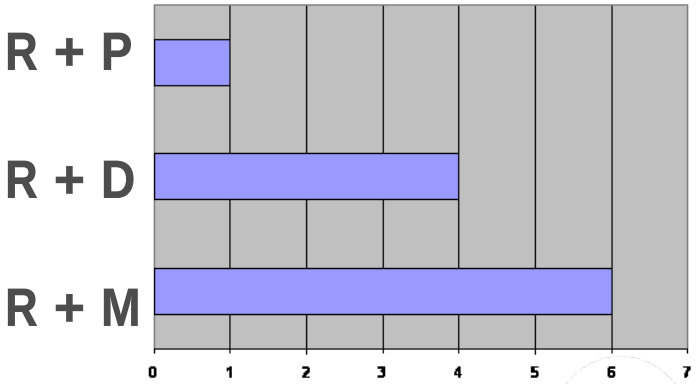
NcWG (30):



Opinions (10):



Two species/PIP (11)



Juvenile Animal Studies
Expected outcomes

- **Additional information:**
  - New/unexpected toxicities
  - Effects on growth and development that were not studied in previous Nc studies
  - Reversibility
  - Different sensitivity (pharmacodynamy and/or toxicity)
  - Different PK profile

- **Usefulness:**
  - Were the results predictable from the known pharmacology?
  - Were the results predictable from the results in the adult?
  - Was there any added value for the paediatric trials?
  - Was there any changes to the product label?

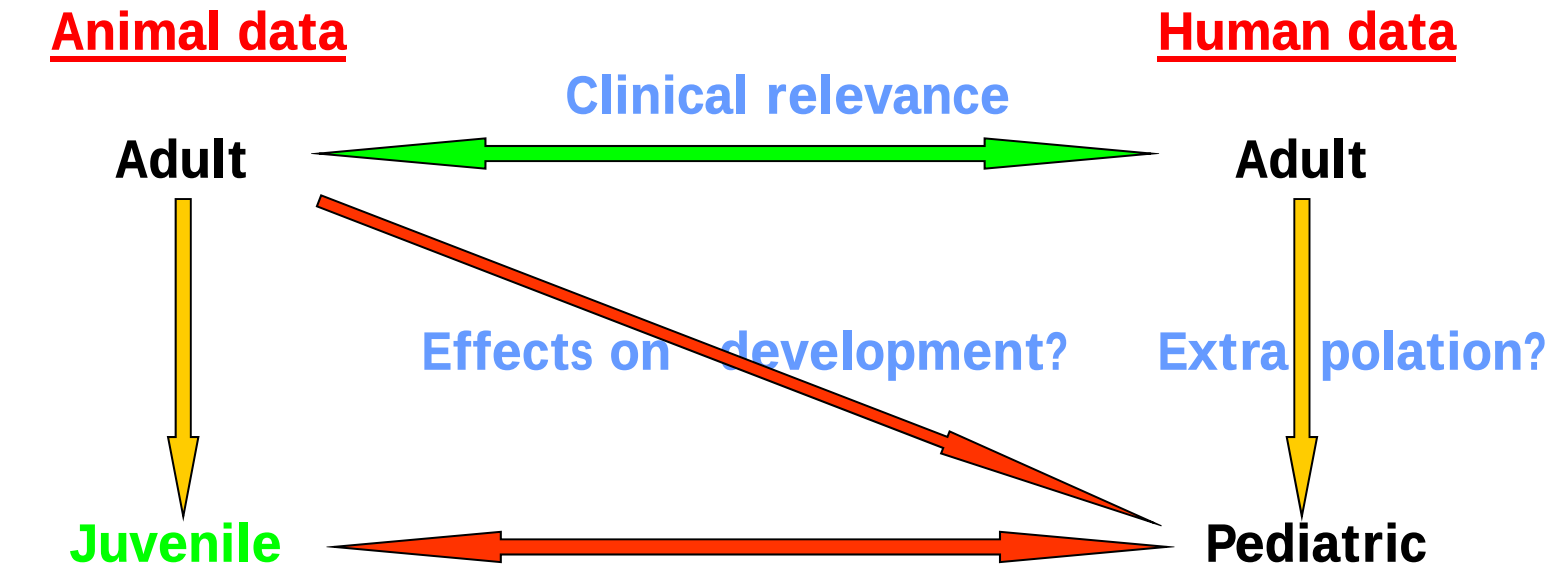
What we have learned from pre-clinical juvenile toxicity studies? (Bailey GP, Marïen D-2009)

Sensitivity	N. of studies(n=39)	Indications
Much less sensitive than adult	1	respiratory
Less sensitive than adult	1	CNS
Comparable to adult	27	All
More sensitive than adult	9	3 anti-infect. 2 GI tract 2 CNS 1 BP 1 respiratory
Much more sensitive than adult	1	anti-infective

- **4 cases of novel toxicity were observed**
- **In 20% of the cases: Nc work contributed to the paediatric clinical trial**
- **In 30% of the cases: Nc work contributed to product labelling**

Questions

- **Are we on the right track?**



(from same class of compounds)

More data needed:

- **Extrapolation: from adult to juvenile /paed., animal to man, juvenile to paediatric**
- **Are the juvenile studies predictive enough? (missed tox)**
- **Need for new Nc models (particularly for efficacy)?**

Thank you for your attention!

When is a PIP not needed?

- Authorised products that do not have a valid Supplementary Protection Certificate (SPC) or a valid patent that qualifies for it. (i.e. off-patent products already authorised in the EU)

- New medicinal products that belong to some specific groups:
  - Herbal medicinal product
  - Homeopathic products
  - Generic products
  - Hybrid products
  - Biosimilar products
  - Well-established use

- Class-waivers:

  For a class of products in a condition

  For all products in a condition

Non-clinical Testing in Juvenile Animals (CHMP/SWP/169215/2005)

Key Elements for the Need for Juvenile Animal Studies:

· There is insufficient human and animal data for a safety evaluation in the intended paediatric age group.

· Findings in non-clinical studies indicating:
  · toxicity relevant for developing systems,
  · potential for effects on growth and/or development in the target age group.

· Concerns on a pharmacological effect to affect developing organ(s).

Non-clinical Testing inJuvenile Animals (CHMP/SWP/169215/2005)

Key Elements for the Need for Juvenile Animal Studies (cont'd):

· Concerns on pharmacokinetic differences in adults and paediatrics.

· There is a specific concern predicted in adults needing further
  · study of reversibility,
  · understanding of possible aggravation of the expected findings,
  · safety factors to be established.

Paediatric Regulation (EC) N° 1901/2006

Non-clinical working Group work schedule

Issues identified by Coordinator/rapporteur, fill out request form (first page of the non-clinical evaluation form)

Request sent to group by end of Day 30 PDCO

Secretariat will allocate PIPs to non-clinical assessors

Evaluation form filled out by non-clinical assessor

NcWG meeting: Week before Day 60 PDCO

Outcome of the discussion: recomendations to PDCO

- Causes for concern indicated in the SR
- Request for modifications

Non-clinical Testing inJuvenile Animals (CHMP/SWP/169215/2005)

General considerations:

- The need for Juvenile animal studies are considered **case by case**

- When the target population is very young Juvenile animal studies are usually considered

- The study designs are case-dependent

- Adapted Pre- Post natal studies are being considered as adding to or as alternative to juvenile animal studies

- The 3Rs principles are taken into consideration