Belgian Federal Agency for Medicines and Health Products (FAMHP)

European Union Regulatory Perspective

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05.May.2010
DISCLAIMER

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Non-clinical Regulatory Framework

Regulation on ‘Medicinal Products for Paediatric Use’
(EC) No 1901/2006
Jan 2007

Guideline on the ‘Need for Non-clinical Testing in Juvenile 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

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: age adapted form.
  • Safety: Non-clinical: juvenile studies?
  • Efficacy: Clinical: studies and timelines

Marketing
Authorisation
Criteria

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

- **Timing:** for a new medicinal product under development

![Paediatric Investigation Plan Diagram]

- **Phase 1**
- **Phase 2**
- **Phase 3**
- **Post approval**

**Adaptation of non-clinical development**

**PIP submission**

**PIP amendments**

**Adult MA**

**Paed. MA**

**CC**

**MA**

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.
- 1 member + 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)

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 PDCO
  • Additional nonclinical experts on a case by case basis
  • EMEA coordinators

• Outcome: recommendation to the PDCO

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

- **Day 1**: Summary Report
- **Day 30**: 1st PDCO discussion
- **Day 60**: Stop clock
- **Day 90**: 3rd PDCO discussion
- **Day 120**: Adoption of Final Opinion

**NcWG meeting:** Week before PDCO

**Timeline:**
- 60 days
- ~3 months
- 60 days

**Key Events:**
- Day 1
- Day 30
- Day 60
- Day 61
- Day 90
- Day 120
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 in Juvenile 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 in Juvenile 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.

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.

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)

- Genetics
- Neonatology-Paediatric intensive care
- Ophtalmology
- Gastroenterology-hepatology
- Pain-Neurology
- Uro nephrology
- Other
- Dermatology
- Neurology
- Pneumology-allergology
- Psychiatry
- Cardiovascular diseases
- Haematology-Hemostaseology
- Rheumatology-Immunology-Transplantation-Oncology
- Endocrinology-Gynaecology-Fertility-Metabolism
- Infectious disease
- Oncology
Non-clinical working group statistics (Nov 2008-Oct 2009)

Age distribution proposed by the applicant

(-neonates: n=16)

PIPs (n=97)
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

- **Oncology**
  - Proposed by the NcWG: 10
  - Done/planned by the applicant: 2

- **Infectious diseases**
  - Proposed by the NcWG: 8
  - Done/planned by the applicant: 6

- **Endocrinology**
  - Proposed by the NcWG: 4
  - Done/planned by the applicant: 4

- **Rheumatology**
  - Proposed by the NcWG: 6
  - Done/planned by the applicant: 2

- **Cardiovascular diseases**
  - Proposed by the NcWG: 2
  - Done/planned by the applicant: 0

- **Haematology**
  - Proposed by the NcWG: 1
  - Done/planned by the applicant: 1
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):
- Pig
- Mouse
- Monkey
- Dog
- Rat

NcWG (30):
- Pig
- Mouse
- Monkey
- Dog
- Rat

Opinions (10):
- Pig
- Mouse
- Monkey
- Dog
- Rat

Two species/PIP (11):
- R + P
- R + D
- R + M
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 (pharmacodynamics 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, Mariën D-2009)

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

- 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?

Animal data

Clinical relevance

Human data

Adult

Effects on development?

Extrapolation?

Juvenile

(Pediatric

(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 in Juvenile 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.

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: recommendations to PDCO
Causes for concern indicated in the SR
Request for modifications
Non-clinical Testing in Juvenile 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