EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# SME workshop: Focus on non-clinical aspects

Session 1:

## *Pre-clinical Requirements to Support Development of Paediatric Medicines*

03 October 2016, EMA

Presented by: Janina Karres, PhD
Paediatric Medicines - Product Development & Scientific Support Department

- Timing, Guidelines, Study Designs
- European Paediatric Regulation
- EMA Experience
- Interactions with Regulators

- Timing, Guidelines, Study Designs

European Paediatric Regulation

EMA Experience

Interactions with Regulators

# Timing and Guidelines

EUROPEAN MEDICINES AGENCY

## Guideline: *ICH M3; CPMP/ICH/286/1995 (R2)*

**Before initiation of trials in paediatric populations:**

### Non-clinical data

- Repeated-dose toxicity studies
- Safety pharmacology package
- Genotoxicity tests
- Reproduction toxicity studies
- Carcinogenicity testing prior to long term exposure, *if cause for concern*
- Juvenile animal studies, *case by case basis*

### Clinical data

- Safety data from adult exposure

# Children are not small adults

EUROPEAN MEDICINES AGENCY

Human organ development:

Liver: up to 1 year of age

Kidneys: up to 1 year of age

Lung: up to 2 years of age

Immune system: up to 12 years of age

Brain: up to adulthood

Reproductive system: up to adulthood

Skeletal system: up to adulthood

Children may be more sensitive to drugs than adults because of:

- ***unique toxicity to developing systems***
- ***immaturity of detoxification mechanisms***

# Need for juvenile animal studies?

EUROPEAN MEDICINES AGENCY

Guideline: *Need for non-clinical testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications,* CHMP/SWP/169215/2005, *adopted* 2008

Important considerations:

- Age of human paediatric target population?
- Target organ toxicity in adults in tissues that undergo significant postnatal development?
- Is the drug target involved in important developmental pathways?
- Specific safety concerns in adults needing further:
  - study of reversibility?
  - understanding of possible increased sensitivity of identified toxicities?
  - establishment of safety factors?
- Chronic or acute therapy?
- Availability of class data

# Juvenile animal study design considerations

EUROPEAN MEDICINES AGENCY

**Selection of species (in general one species, M&F)**

Appropriate for evaluating toxicity endpoints relevant for the paediatric target population (PK;PD; toxicology; species sensitivity).

**Endpoints**

Depend on safety concerns. May include: *clinical signs, bodyweight, food consumption, organ weight, histopathology, TK, bone/growth (BMD, femur length,…), ophthalmology, clinical chemistry, hematology, necropsy, neurobehavior (learning, memory,…), sexual maturation landmarks*.

**Dose Selection**

Short term juvenile dose-range finding (DRF) study incl TK may help determine dosing regimen for definitive juvenile study.

Establish dose-response in low dose range (NOAEL or NOEL).

High dose should achieve some identifiable toxicity, but not result in marked toxicity.

Low dose should result in anticipated clinical exposure.

# Juvenile animal study design considerations

EUROPEAN MEDICINES AGENCY

**Route of Administration & Dosing Regimen**

Ideally, same as intended human route.

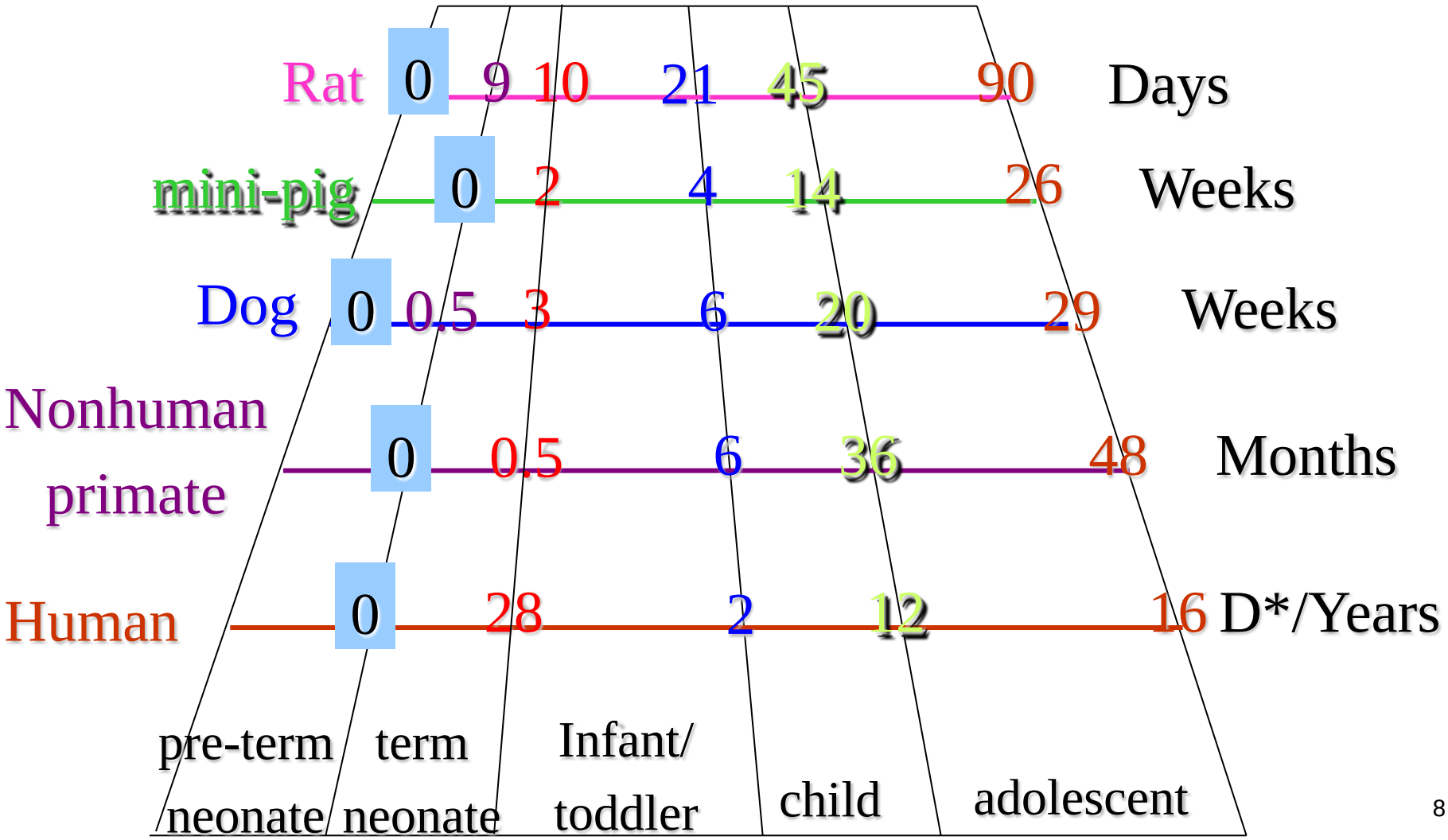
Dosing regimen & route of administration of the JAS should be aligned with the comparative adult pre-clinical studie(s) and should consider the anticipated clinical dosing regimen.

**Duration of dosing period and age of animals at start**

Dependent on expected target organs & age of paediatric target population.

- Short term developing systems (lung, kidney): study confined to development period.
- Long term developing systems (brain, bone, etc): study up to adulthood.
- Evaluation of reversibility or long-term consequences of potential adverse reactions should be considered.

## Comparative Developmental Stages



Timing, Guidelines, Study Designs

- European Paediatric Regulation

EMA Experience

Interactions with Regulators

# January 2007: EU Paediatric Regulation

**(REGULATION (EC) No 1901/2006 on medicinal products for paediatric use)**

## Objectives

Improve the health of children:

- Increase high quality, ethical research into medicines for children
- Increase availability of authorised medicines for children
- Increase information on medicines

Achieve the above:

- Without unnecessary studies in children
- Without delaying authorization for adults

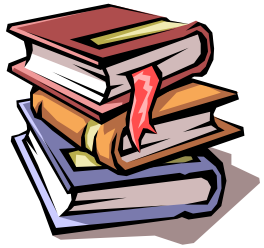
# Paediatric Investigation Plans (PIP)

Research and development programme

Details timing & measures for paediatric indication

Quality
Pre-clinical
Clinical

**Marketing Authorisation**



Timing of PIP application: **after completion of adult phase I clinical trials**

*Binding upon company!*

# Non-clinical Working Group of PDCO

EUROPEAN MEDICINES AGENCY

## Mandate

- Support the PDCO in the review of the Nonclinical section of PIPs.
- Recommendations to the PDCO on pre-clinical requirements to support paediatric clinical development.

## 16 NcWG Members

- Chair: Jacqueline Carleer
- 2 members from the PDCO
- 5 members from SWP
- 3 observers from the FDA

## Where do NcWG members come from?

- All members come from National Authorities

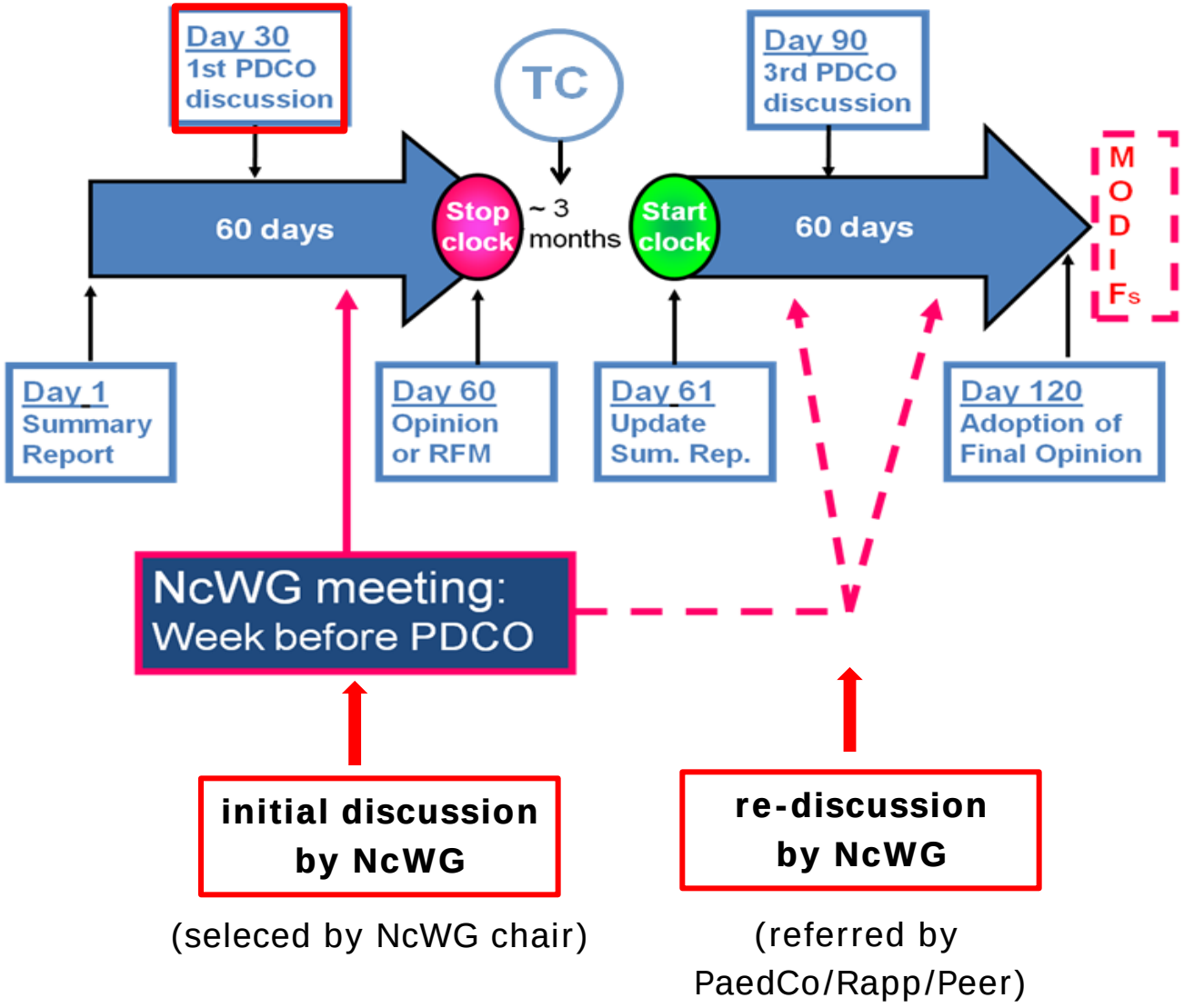
## Meetings

- Virtual meeting once a month, one week before PDCO plenary
- Once a year face-to-face meeting at EMA

# Non-clinical Working Group

EUROPEAN MEDICINES AGENCY

## How does the group work?



# The NcWG Review Process

**Review of**:

- Non-clinical data and available clinical safety data.
- Proposed non-clinical strategy (including pharmacology, toxicology, toxicokinetics) to support development of paediatric medicines.

**Review Process and Conclusion**:

- Reviews to be based on scientific evidence resulting in a statement of clear concerns and requests to the applicant on the need for specific measures.
- Reviews not to be limited to specific therapeutic fields and types of products but cover all to ensure the safety of children in paediatric trials.

Timing, Guidelines, Study Designs

European Paediatric Regulation

- EMA Experience

Interactions with Regulators

# EMA Experience: PIP

EUROPEAN MEDICINES AGENCY

**Juvenile animal studies included in PIPs (analysis of PIP data: 2008-2016)**

About **26%** of PIPs contain **juvenile animal studies**.

**71%** of PIPs which contain juvenile animal studies were intended for a target population including children **2 years** of age or younger.

**43%** of these PIPs included **neonates**.

The majority (**80%**) of these PIPs contained only **one definitive juvenile study**.

Out of these, **76%** are in the **rat**, 6% in mouse, 8% in dog and 10% in the monkey.

About **4%** of PIPs contained juvenile studies in **more than one species**.

# EMA Experience: PIP

EUROPEAN MEDICINES AGENCY

**Juvenile animal studies inform human paediatric drug development and contribute to safeguard children**

| | Full Waiver (for *all paediatric age groups*) | Partial Waiver (*only for certain age groups*) |
|---|---|---|
| **PIP Opinions with waivers based on safety** | **5.2%** (46) | **9.4%** (83) |
| ↓ | ↓ | ↓ |
| *% of those where decision was based (mainly/also) on results of* ***juvenile animal toxicity studies*** | 17% (8) | 22% (18) |

Legend:

( ) = Total numbers of PIP opinions with waivers based on safety grounds.

Of note, the total number of PIP Opinions at time of analysis was 881.

# Oncology project

EUROPEAN MEDICINES AGENCY

## Analysis of juvenile animal study reports for 19 anti-cancer medicines

(mostly targeted therapies such as TKI's etc)

**Results:**

- 8 cases: **new target organ toxicities** (growth, behaviour, bone, **brain, eye, heart, kidney, lung, nasal cavity,** reproduction organs, spleen, thymus).
- 7 cases: **toxicity** observed **earlier** and/or at **lower** dose/**exposure** level 2 times **down to one hundred times** (associated in 3 cases to higher exposure levels in the younger animals).
- 11 cases out of 15: **exposure level in juvenile animals higher** than in adults (X 2-13). In two case doses were adapted to reach constant level. In three cases this hampered the data interpretation.
- 2 cases: the study started with rats **aged** 21PND to support the treatment of either neonates or 1y old infants.
- 1 case: **different dosing regimen** in juvenile and adults hampered the interpretation.

*(slide adapted from Jacqueline Carleer)*

# Oncology project

EUROPEAN MEDICINES AGENCY

**Regulatory outcome:**

- 3 cases: PIP change: waiver
- 3 cases: PIP change: deferral
- 2 cases: clinical protocol changes (doses, escalation, monitoring)
- 9 cases: MA submission and results incorporated into the smpc, with in two cases a warning/contraindication

*(slide adapted from Jacqueline Carleer)*

# Oncology project

EUROPEAN MEDICINES AGENCY

**Lessons learned:**

- **Juvenile toxicity studies revealed serious specific safety issues which may have been life threatening for the youngest patient population 3/19).**
- **Juvenile toxicity studies revealed unexpected toxicity (9/19), several not related to primary pharmacology or observed in adults.**
- **When serious safety concerns arise, waivers are generally requested for the youngest patient population where medical needs are. More efforts should be undertaken to understand the clinical relevance.**
- **Importance of TK! Need for dose adaptation?**
- **It is hasardous to extrapolate results from one multi-TKI to a « similar » one.**

*(slide adapted from Jacqueline Carleer)*

Timing, Guidelines, Study Designs

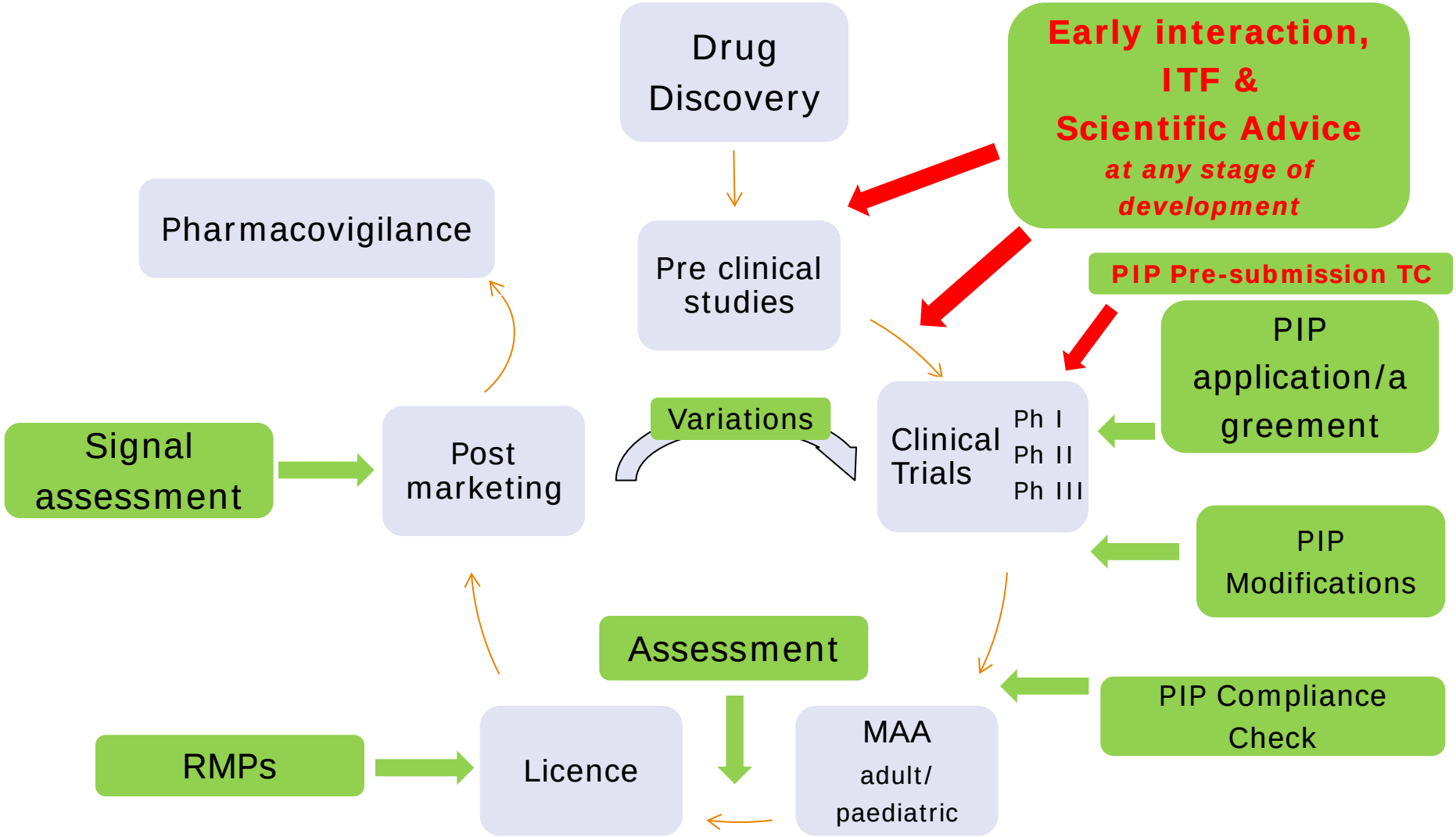
European Paediatric Regulation

EMA Experience

- Interactions with Regulators

# Interactions with Regulators

EUROPEAN MEDICINES AGENCY




Adopted from Health Canada

# Timing: very early stages of development

(before end of phase I adult development)

Discussion on general development strategy:

- Properties of the future medicinal product and its potential overall development.
- Potential paediatric needs
- Scope of development (condition): PIP or Waiver?
- Quality: need for paediatric formulation?
- **Pre-clinical: need for juvenile study?**
- Clinical: patient population, endpoints, study duration, controls, extrapolation?
- Raising awareness on specific paediatric issues/ difficulties known to occur during development.

# Timing: early stages of development

Forum for early dialogue for innovative therapies and technologies incl ATMPs, nanomedicines, ……

Aim:

Facilitate informal exchange of information and guidance in the development process, complementing and reinforcing existing formal regulatory procedures.

Scope:

Regulatory, technical and scientific issues arising from innovative medicines development, new technologies and borderline products

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800ba1d9&jsenabled=true

# Scientific Advice (SA)

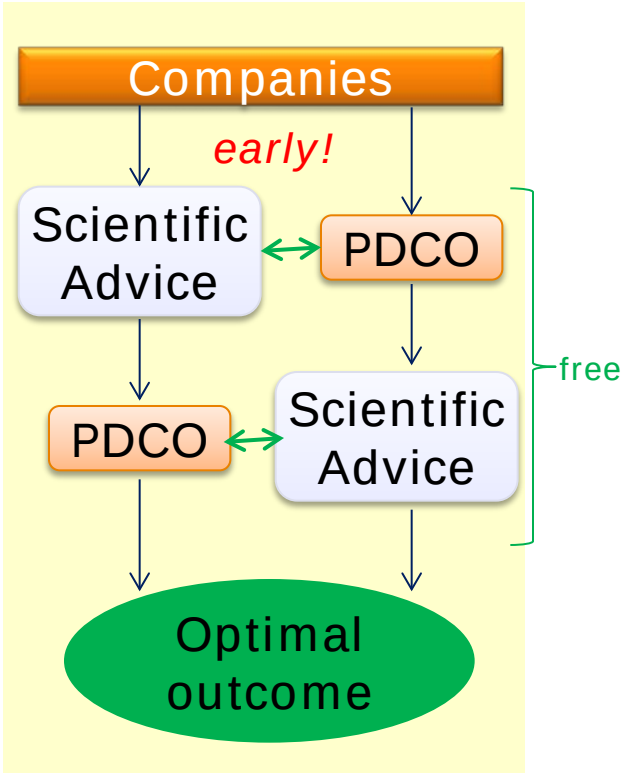
EUROPEAN MEDICINES AGENCY

The committee/authority in charge:

- **EMA- SAWP/CHMP**
- **NCA- relevant departments**
- For EMA SA, liaison with **PDCO** for questions on paediatric development.

Optimal strategy:

- SA procedure on paediatric program *before* submitting PIP.
- But SA can be requested at *any stage of development*.
- Recommended especially for *novel medicinal products, studies with innovative methodology/designs, endpoints,rare disease…*
- The outcome of a paediatric SA will be thoroughly considered by PDCO during PIP assessment.



# PIP Presubmission Meeting

EUROPEAN MEDICINES AGENCY

## Timing: when PIP is nearly ready for submission

Objective: ensure smooth PIP validation procedure.

Participants: EMA, PDCO representative

Discussion of draft PIP application and list of questions:

- Level of detail as regards information on paediatric quality, pre-clinical, clinical development.
- Highlighting potential issues as regards chosen condition, age/severity subsets, study designs, ..

# Conclusions

EUROPEAN MEDICINES AGENCY

- Need for juvenile animals studies to be evaluated on case- by-case basis, considering all relevant available (pre-)clinical data.
- Juvenile studies can inform human paediatric drug development and contribute to safeguard children.
- Juvenile animal study designs need to be tailored based on (potential) safety concerns/target organs of toxicity and the intended paediatric population.
- Short term juvenile dose-range finding (DRF) study incl TK may help determine dosing regimen for definitive juvenile study.
- Evaluation of reversibility or long-term consequences of potential adverse reactions should be considered.
- Several (early) interactions with regulators are possible. SA is free of charge if questions only relate to paediatric development. Take advantage!