Human and veterinary pharmaceuticals regulation

Towards EU accession: Serbia's regulatory challenges, expectations and opportunities

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Republika Srbija
Ministarstvo zdravlja
Ministarstvo poljoprivrede, šumarstva i vodoprivrede,
Uprava za veterinu

Republic of Serbia
Ministry of Health
Ministry of Agriculture, Forestry and Water Management,
Veterinary Directorate

alims
Agencija za lekove i medicinska sredstva Srbije
Medicines and Medical Devices Agency of Serbia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Paediatrics: Paediatric Investigation Plan

National Agency Assessor's Point of View

Presented by: Dr Ljiljana Milosevic-Kapetanovic
Afssaps, France

EC Twinning Project 2006-2009

-Relation between ALIMS/MoH and Afssaps within twinning project

-Institutional and Capacity Building of ALIMS

-19 activities

-Workplan: training on clinical assessment but no topics in paediatrics

EU Paediatric Regulation

(EC) N° 1901/2006

- **Official Journal of the EU** (27.12.2006.)
- **Objectives:**

  - facilitate the development and accessibility of MP for use in the paediatric population

  - ensure that these MP are subject to ethical research of high quality, appropriately authorised for use in paediatric population

  - improve the information available on use of MP in various paediatric population

EU Paediatric Regulation

(EC) N° 1901/2006

•Creation of a Paediatric Committee (PDCO) within the European Medicines Agency: to provide objective scientific opinions on any development plan for medicines for use in children

- primarily responsible for scientific assessment and agreement of PIP and for the system of waivers and deferrals

- members should not have financial or other interest in pharmaceutical industry

EU Paediatric Regulation

(EC) N° 1901/2006

- Without unnecessary clinical trials in children

- Without delaying the autorisation of MP for other age populations

PIP: Paediatric Investigation Plan

Definition:

« Research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a MP may be authorised to treat the paediatric population »

Paediatric population:

- between birth and 18 years

PIP: Paediatric Investigation Plan

- Integral part of the development programme for adults, binding on company

=> should be submitted early during product development (end phase I studies in adults)

- submission of paediatric data
- deferral request: to avoid delaying MA
- waiver: possibility case by case

PIP: Requirements

PIP submission:

- New medicinal products
- Authorised medicinal products covered by a patent or suppl protection certificate
- Authorised MP not covered by a patent or SPC (PUMAs)

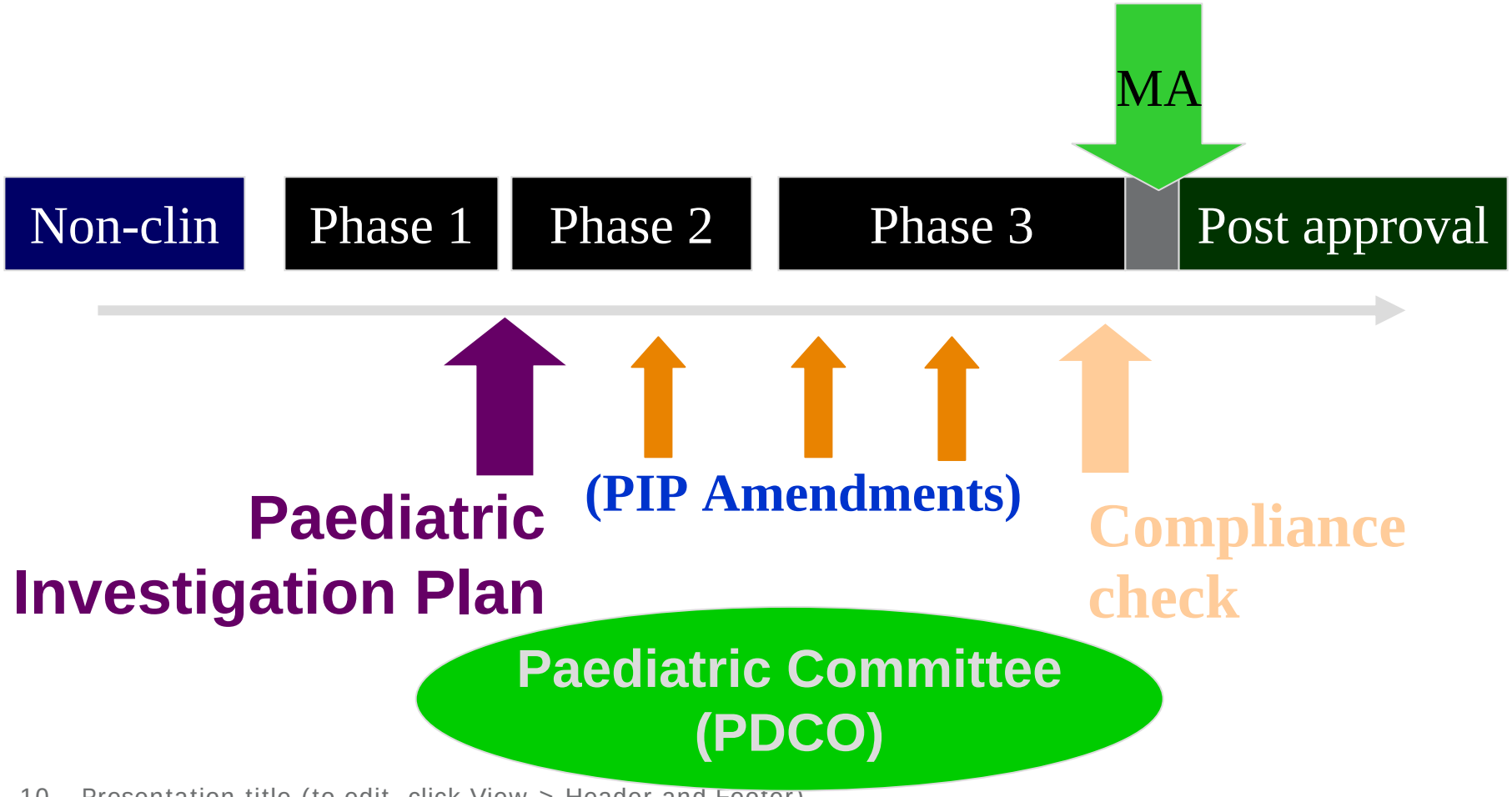
Exclusion:

- Generics
- Biosimilars
- Well-established use
- Homeopathic/ traditional herbal MP
- Class-waivers

PIP: Request for Agreement

- **Application for MA** in accordance with:
  - **art. 7** (new medicinal product)
  - **art. 8** (authorised MP): new indications, including paed indications, new pharmaceutical forms and new routes of administration
  - **art. 30** (PUMA: paediatric use marketing authorisation): MA granted for MP not protected by a SPC

When should the PIP be requested?



PIP: Agreement and Reward

- **Reward**: for conducting paediatric studies, not for demonstrating safety/efficacy of product in children

  =>new MP: data exclusivity prolongation (6-month extension of suppl protection certificate) even when paed indication is not authorised

  =>at least, relevant information in the SmPC

- When PIP is agreed with indication approved, the MAH obliged to place the product on the market within 2 years of date of approval paed indication

Clinical Trials on Paediatric Population

- Performed in children from birth up to the legal age of adulthood
- Vulnerable population (pain, fear, distress, parental separation) => need to balance B/R of research in children
- Trials are necessary for progressing well-being, treatment, prevention and diagnosis
- CT carried out under conditions affording the best possible protection

Grounds for Product-Specific Waiver

1. Medicinal product is likely to be ineffective or unsafe in part or all paediatric subgroups
2. The disease or condition occurs only in adult populations
3. MP does not represent a significant therapeutic benefit over existing treatments

Possible partial waiver for specific age-subsets with justifications

List of class waiver: EMA website

PIP Assessment

Deadlines!

=> Summary Report to be prepared within 30 days following receipt of the request (30 days more if need for supplementary information)

PIP Procedure

Day 0 - PIP + Summary Report (EMA Paediatric Co-ordinator)

PDCO → **PDCO** → **PDCO**

Day 30 - Comments SR Rapporteur / Peer-reviewer

Day 60 - Discussion Opinion or clock stop

PIP Assessment

In addition:

- **Modifications:** changes, request for deferral, waiver

- **Compliance check** (EMA or NCA): verification whether an application for MA or variation comply with the agreed PIP

=>OPINION within 60 days

PIP in MAA

- During MAA assessment:

  - If the submitted studies not in conformity with the agreed PIP

  => the product not eligible for rewards and incentives

- If deferral after completion CT in adults:

  => delay of CT in children (may be too long)

PIP Structure I

- **A**: **Administrative and product information**
- **B**: **Overall development** of the medicinal product
  - Pharmacological rationale
  - Target disease/condition and paediatric specificities
  - Current methods: diagnosis, prevention, treatment
  - Therapeutic needs by age groups
  - Therapeutic benefit of the product vs alternatives

-> Similarities/differences between adults and children

PIP Structure II

•**C**: **Waiver request** with grounds for a product-specific waiver based on:

- lack of efficacy and safety

- disease/condition not occuring in the specified paediatric subset(s)

- lack of significant therapeutic benefit

•**D**: **Development plan**: Quality, non-clinical, clinical, timelines

•**E**: **Request for deferral**

Elements for PIP Assessment

D: PIP with clinical development

⇒**Quality** aspects of the product to be established with adapted paediatric formulation

⇒**Non-clinical** aspects with protocols of planned and/or ongoing non-clinical studies

⇒**Clinical** plan with description of all planned and/or ongoing clinical studies

PIP: Formulation Development

-Age-appropriate formulation

-Preferable: liquid oral dosage forms

- can be safely swallowed
- excipients!
- flavouring agents

PIP: Pre-clinical Assessment

- Toxicology, genotoxicity, carcinogenicity
- In vitro, in vivo studies

=>Need for juvenile animal studies?

=>Species and age of animals appropriate?

PIP: Clinical Assessment

- **Development programme in adults**: PK/PD studies, dose-finding study

  -> Data extrapolation?

- **Proposed dosing regimen** in children: according to weight, BSA

- **Efficacy / safety studies** in appropriate subsets of paediatric population

- **Design of clinical trials**: comparator, endpoints, duration, long-term follow-up

Paediatric information on established risk/benefice

- **Objectives of a MAA**

  - Labelling of paediatric therapeutic indications

    => section 4.1. of the SmPC

  - Dosing regimen, according to age sub-sets

    => section 4.2. posology

  - Safety information in sections 4.4., 4.8. (4.3.?)

  - If paediatric data not sufficient for full labelling: information on data in section 5.1.

Guidelines

- EMEA Guideline on Pharmacovigilance in Paediatric population
- Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11)
- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (CHMP/EWP/147013/04)
- Guideline on the need for Non-Clinical Testing in Juvenile Animals for Paediatric Indications CHMP/SWP/169215/05

Guidelines

- Guideline on Clinical Trials in small populations CHMP/EWP/83561/05
- Guideline on the investigation of Medicinal Products in the term and preterm neonate
- Reflection Paper on Formulations of Choice in Paediatric Population EMEA/196218/05

Paediatric Organisation in Afssaps (before 2007)

•**COP**: national paediatric comittee

- External/internal experts, pluridisciplinary

=>2001: **Documents on therapeutic needs** for paediatric products with priorities for research

->sent to Paediatric Expert Group (EMEA)

- Opinions on paediatric topics (hospital preparations, temporary authorisations)

•Referential for investigators' training on CT (paediatric part)

Paediatric Investigation Plans Assessment in Afssaps

- **Changes in 2007:**
  - **set up of Paediatric Unit**
  - **creation of PIP Working Group, separated from COP**

www.afssaps.fr/activites/medicaments-en-pediatrie

PIP Assessment in Afssaps

- **Paediatric Unit**: 2 evaluators + head of unit
  - transvers collaboration with other units
  - 2008: 64 PIPs (Rapp, Peer); 1 modification
  - 2009: 52 PIPs; 13 modifications
- French representatives in PDCO

PIP Assessment in Afssaps

- **PIP Working Group**: expert group (paediatricians, galenic, toxico, PK/PD, specialists onco-hemato, neuro, cardio, PV)

  - monthly meeting, contribute to PIP assessment (when France Rapp/Peer-reviewer)

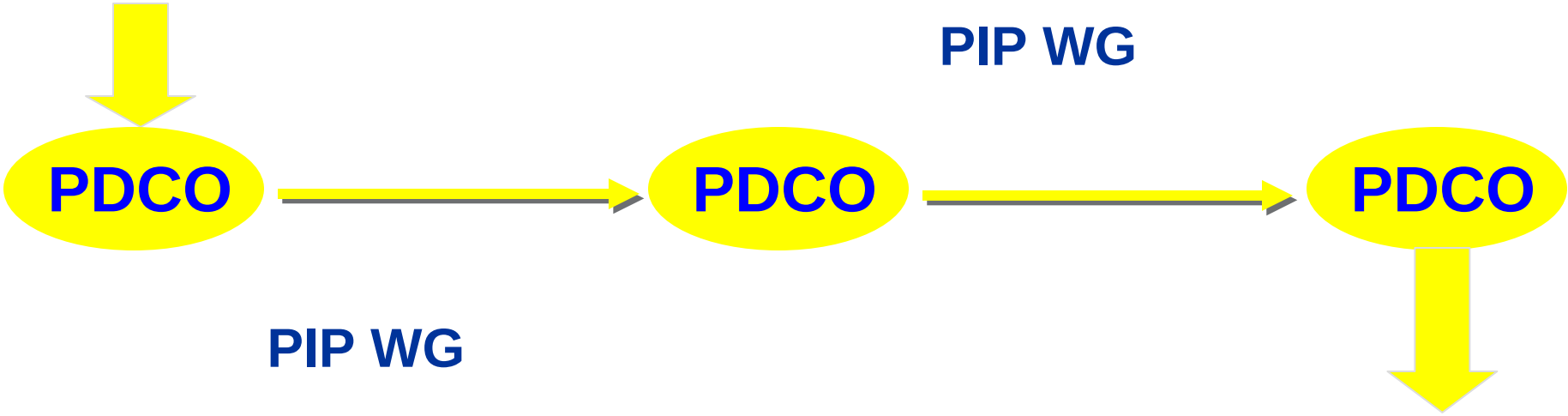
  =>opinion on other PIPs selected for comments

  =>interactions with Afssaps departments: scientific advice, pharmaceutical, pre-clinical, PK/PD, PTC Units, bio, safety

PIP Procedure and WG activity: short deadlines

Day 0 PIP + Summary Report

D40 Discussion PIPs Comments France



D10 Discussion 3-4 PIPs France rapporteurship

Day 60 Decision on PIP or clock stop

Paediatric Worksharing

- Assessment of paediatric data in the frame of articles 45 and 46 EC Paediatric Regulation (old CT and new CT 6m after completion)

=>Submission by MAHs of all available data in children for 1000 medicinal products, including generics, herbals etc.

=> Data assessment of the competent authority (Rapp); long process to assess all MP (10y)

=>Paediatric information: SmPC; PL

Interaction with Pharmaceutical Industry

- How the new paediatric regulation affects both the work of regulators and industry?

1. Regulators: new organisation, deadlines, concept of PIP SR template
2. Difficulties for Industry?

Interaction with Pharmaceutical Industry: Lessons Learned

- For companies:
- paediatric development must now be an integral part of the product development
- Paed development to be anticipated in the timelines of the product development, to plan MAA, variation, extension, submission
- Being compliant is a requirement for validation!

(EMA origin)

CT Research Network in France

- **CeNGEPS**: national centre for management of trials on health product trials, set up in 2007, brings together the main public and private clinical research operators (www.cengeps.fr)

=> initiative for more effective clinical research in France

=> objective “to recruit much, much faster and better” in industrial CT by simplifying the procedure for setting up trials

Paediatric Research Network in France

- **RIPPS**: investigation network for paediatric health products (www.ripps.eu) created in 2005, part of EU network coordinated by the EMA
- **CIC:** paediatric network of clinical investigation centers created in 2000 (www.cic-pediatriques.fr)

=> interactions between researchers, paediatricians and pharmaceutical industry

=>appropriate expertise, facilitation of paediatric CT, guarantee of the quality of the investigations

CONCLUSION

- **Ethical considerations** of CT

  ->Children are not small adults!

  ->Avoid unnecessary studies, modeling of CT

- **Therapeutic needs** for paediatric data within PIP applications

  ->appropriate studies in children in appropriate age subsets

  ->adapted paediatric formulation

  ->juvenile studies