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Collaboration and exchange of information between the COMP and the Paediatric Committee

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What do the COMP and PDCO have in common?

Both Committees are created as a result of concern by the Commission that market forces alone had proven to be an insufficient incentive for adequate research, development and authorisation of medicinal products in distinct groups of patients in casu the paediatric population and the patients with rare and/or seriously debilitating chronic condition.

Fees to be paid to the Agency by the sponsors of orphan medicinal products and by the applicants of a Paediatric Investigational Plan are waived

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Double incentive for drugs with an orphan designation developed for children with an agreed and realised PIP

Instead of an extension of the supplementary protection certificate (6m.), the ten-year period of orphan market exclusivity is extended to twelve years if the requirement for data on use in the paediatric population is fully met.

What COMP and PDCO had in common

Number paediatric investigation plan assessed at the PDCO with a orphan designation

107/810

Number of medicinal products assessed at the COMP with a subsequent paediatric investigational plan

107/760

Paediatric Investigation Plan

General strategy of paediatric studies

- Epidemiology, pathophysiology, indications, target population, doses

New formulations (needs & technology) for different subsets of the paediatric population

Preclinical studies (toxicity, effect on pregnancy, juvenile animals)

Clinical studies (PK & dose finding studies, efficacy/safety studies, strategy, timelines)

Waivers and deferrals

Waiver

No need for information of a specific new compound for the obtainment of a marketing authorisation if:

- the disease for which the drug is developed does not exist in children.
- the medicinal product is likely to be ineffective or unsafe
- the medicinal product does not represent a significant therapeutic benefit over existing treatments in paediatric patients

Deferral of clinical studies in children

Although the endpoint of the Paediatric Regulation is to bring nearly simultaneously adult and paediatric medicines on the market:

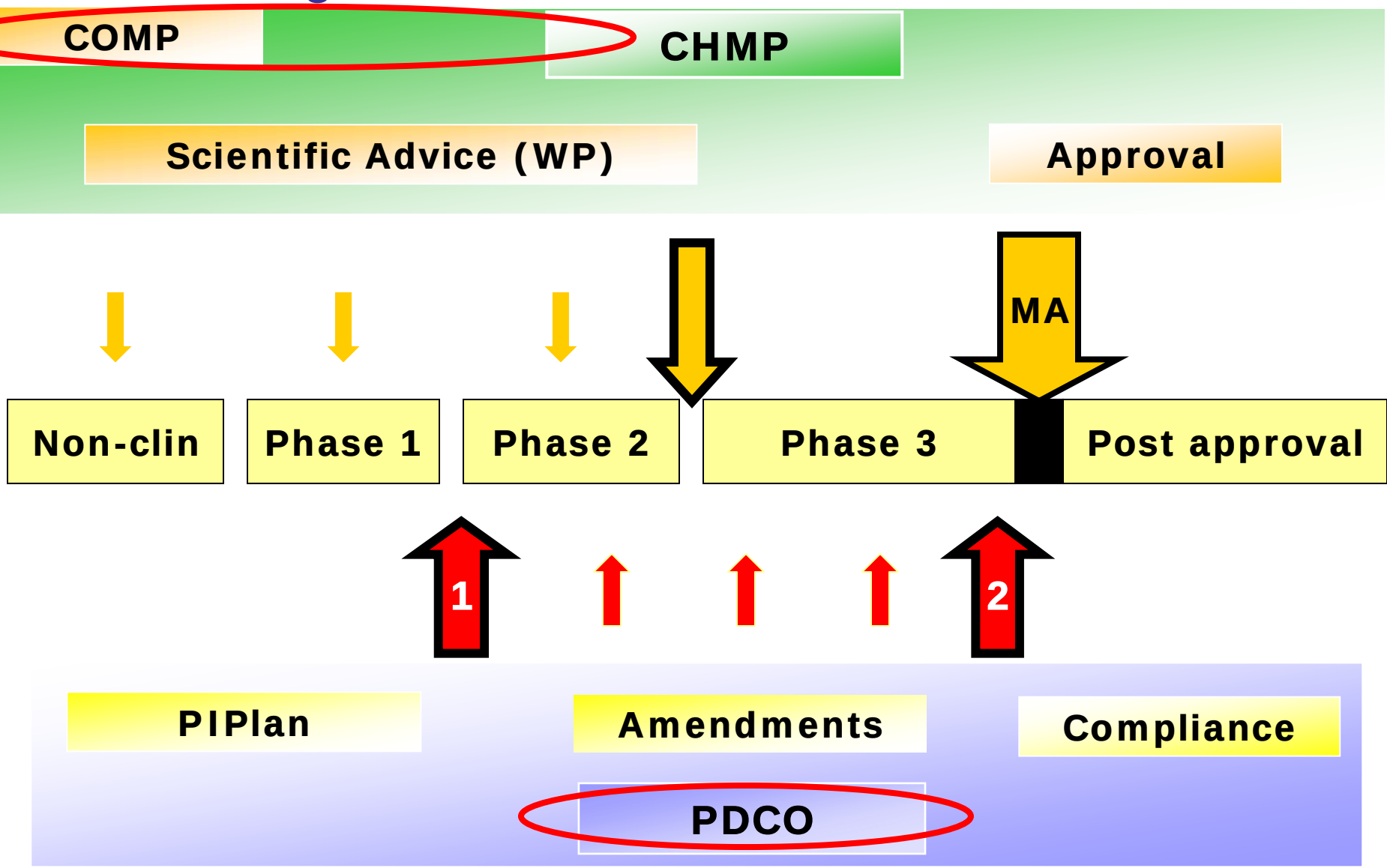
In practice: ethical hurdles exist to embark in paediatric trials of a fully new drug before

- the proof of concept and mechanism of action
- the efficacy
- the safety

is sufficiently established in adults

A staggered approach is preferred, first in adolescents then down to the neonate and preterm

Timing of Consultation of COMP and PDCO



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How to translate the concept of orphan designation into a valuable paediatric investigation plan?

Major hurdles and concerns:

- **low incidence or prevalence**
- **feasibility of clinical trials**
- **expertise and clinical centres of excellence**

Feasibility: how to solve ?

- The condition is rare in the EU but prevalence is high in countries outside Europe (tropical diseases as malaria): PDCO agreed that clinical studies are done exclusively in tropical countries in agreement with the draft of the **REFLECTION PAPER ON ETHICAL AND GCP ASPECTS IN CLINICAL TRIALS CONDUCTED IN THIRD COUNTRIES IN MARKETING AUTHORISATION APPLICATIONS SUBMITTED IN THE EEA**
  - Beta-artemether /lumefantrine:
  - Dihydro-artemesimin-piperaquine for malaria

Feasibility: how to solve ?

- For the same rare condition, several PIP's are submitted for MP that are bio-similars
  - Example: Gaucher disease: SOC=Imiglucerase
    - PIP for
      - Taliglucerase º
      - Velogluc erase

It was agreed at the PDCO on a limited number of patients in phase III clinical studies (30).

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Feasibility: how to solve ?

- Afamelotide is an analogue of α-melanocyte stimulating hormone. It has an orphan designation for a number of extremely rare skin disorders as
  - Erythropoietic protoporphyria
  - Congenital erythropoietic porphyria
  - Solar urticaria

  The PIP proposes a PK/PD study in 28 volunteers 12-17y by means of a bioresorbable implant

  It was agreed at the PDCO that asking healthy children to "volunteer" in painful studies is unethical and unacceptable. Safety and efficacy should first be demonstrated in adults

Feasibility: how to solve ?

- Anagrelide HCl is a platelet lowering agent, selective inhibitor of megakaryocyte maturation indicated in essential thrombocytaemia which is a rare disease (0,1:10.000).
- The applicant proposes to follow up the cases of ET in two centres (N=20) and to treat some of them (total 6).

It was agreed at the PDCO that the number of 6 patients was insufficient. PDCO asked to increase the number of centres to collect data on 48 patients. The registry was welcomed .

Orphan medicinal products and the paediatric priority list of off-patent MP supported by the FP7

- Thiotepa:
  - Orphan designation and on the priority list (2010) as conditioning therapy prior to allo- and auto HSCT for acute leukaemia, Non Hodgkin lymphoma, solid tumours,
- Methotrexate
  - Orphan designation for the treatment of acute lymphoblastic leukaemia
  - Priority list since 2007 for malignant diseases in children since 2009 for Crohn's disease and since 2010 for colitis ulcerosa
- Ibuprofen:
  - orphan designation for open ductus arteriosus in preterm infants <34 w.
  - Priority list since 2008 for PK/PD, and IV formulation in pain

Interaction between COMP and PDCO

The orphan indication for which a medicinal product has an orphan designation may facilitate the PDCO to widen the field of indications as proposed in a PIP:

- Maribavir has an orphan designation for the following orphan indication: “Prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk”. The orphan indication was broader than the proposed therapeutic indication in children, as it includes other conditions beyond bone marrow transplantation: solid organ transplantation, for example liver transplant (for which the company is developing in adults), AIDS and oncology.
- Based on the COMP decision the PDCO could easily convince the applicant to widen its indication.

Interaction between COMP and PDCO

The orphan indication for which a medicinal product has an orphan designation after discussion in the PDCO is proposed to be narrowed to avoid overtreatment:

- Mecasermin rinfabate has an orphan designation since August 2006 for the following orphan indication: “Prevention of retinopathy of prematurity in neonates less than 32 weeks of gestational age”.

- Based on recent epidemiologic studies it appears that ROP is decreasing especially in the age group >30 weeks gestational age due to a more rigorous control of oxygen therapy. To not contribute to bad practice, the PDCO proposed to restrict the indication to the less than 31 weeks GA. This age limit guarantees that the treatment will be restricted to the neonatal intensive care units in Europe.

conclusions

- The target of both committees is common: offer appropriate and safe drugs to those who would have been devoted without EU regulation.
- As a great number of PIPs concerns MP with orphan designation, the need for exchange of information and expertise between members of both COMP and PDCO is obvious. The PDCO as a young committee within the EMA is grateful that it can benefit from the large network of expertise including the patients associations that the COMP has build up in his ten year of existence

congratulations