EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Formulations: PIPs evaluation-case studies

Viewpoint from the EMA - Quality team

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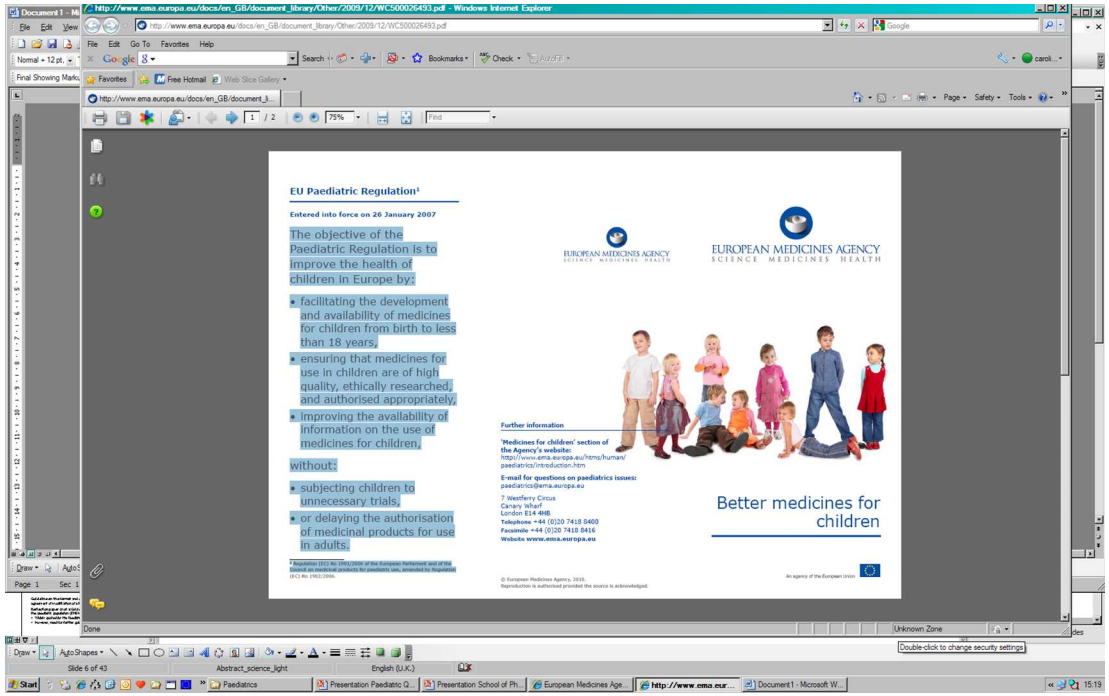
Agenda

- Objective
- Brief background
- Regulatory references
- Evaluation procedure at the Agency
- Case studies
- Conclusion

Objective & Spirit

- To encourage companies to develop specific, 'age-appropriate' paediatric formulations.
- To develop relevant and acceptable formulations with convenient and precise dosing characteristics, on an industrial scale suitable for marketing.
- To present the challenges and issues in relation to Paediatric Investigation Plans (PIPs) and case studies.

Webpage on Medicines for children



Regulatory references

Reflection paper (not a Guideline): Formulation of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005)

- Widely quoted for the Paediatric Formulations.
- However, need for further guidance requested.

Concept paper on the development of a quality guideline on pharmaceutical development of medicines for paediatric use (EMEA/138931/2008).

Regulatory references 2

(Draft) Guideline on pharmaceutical development of medicines for paediatric use

- Collaborative work between QWP, PDCO, and external experts.
- Public consultation aimed very soon.

Regulatory references 3

Guideline on the investigation of Medicinal Product in the Term and Pre-term Neonate (EMEA/536810/2008) – effective from January 2010

- Containing Quality since no Quality GL at the time.
- Formulation aspects specifically for the neonates.

http://www.ema.europa.eu/pdfs/human/paediatrics/53681008enfin.pdf

Regulatory references 4

Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product (CHMP/QWP/396951/06, revised 2008)

- Not to be confused with a separate guideline on safety;
- Warnings relating to specific excipients (i.e. azo dyes).

BUT

mostly with regard to quality standards of the excipients per se, rather than their rational use in suitable formulations.

http://www.ema.europa.eu/htms/human/humanguidelines/quality.htm

Regulatory references 5

Excipients in the Label and Package leaflet of Medicinal Products for Human Use (Eudralex 3BC7A)- to be revised in the long term

- Some excipients not entirely inert – side effects + safety problem
- Excipients should be kept to a minimum, even the so-called 'safe' excipients,

BUT

Safety profiles and warnings based mostly on data in **adults**.

http://www.ema.europa.eu/htms/human/humanguidelines/multidiscipline.htm

References 6

- Food Directives (i.e. Directive 2009/35/EC (colorants in medicines)
- EFSA and CHMP Opinions
- Literature
- External sources (WHO, FDA, Databases, external groups EuPFI…)
- **When evaluating PIP formulations, these references are consulted**

BUT

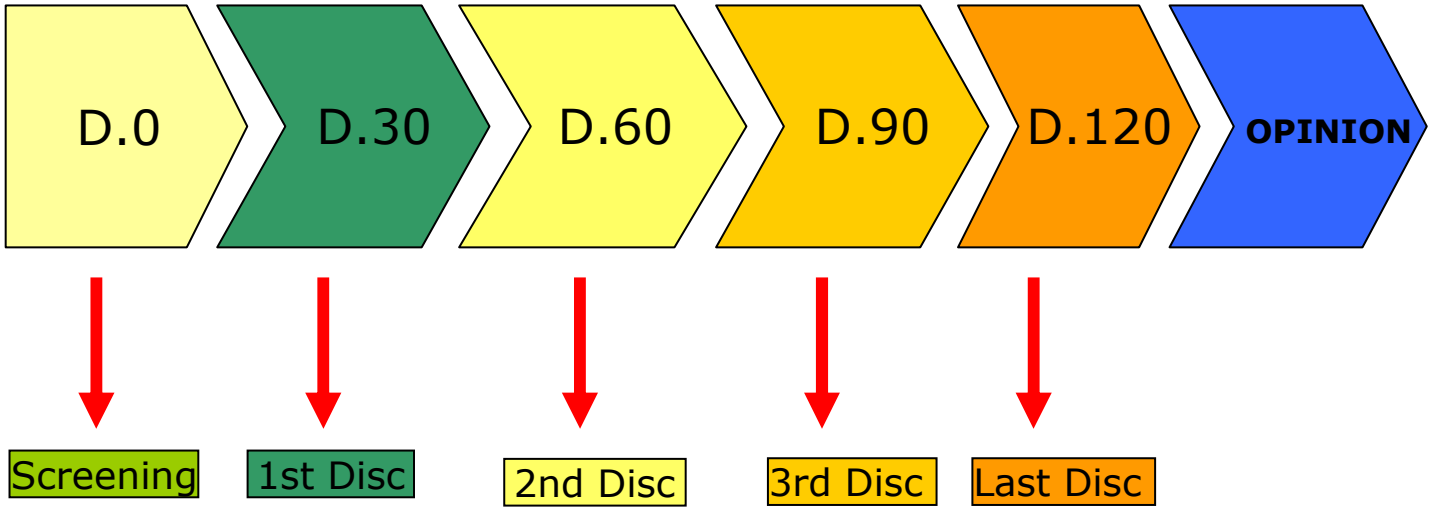
Safety profiles and warnings are based mostly on data in **adults**.

Who we are and what we do ?

- Quality Sector (Chemical & Biologicals)
  - Head of Sector: Dr Alexis Nolte
  - Head of sections: Dr George Wade & Dr Peter Richardson
  - Scientific administrators and Assistants : 32 + 10

- Collaboration with the Paediatric team and PDCO FWG + working parties (QWP, BWP, SWP)

Quality aspects & PIP procedure ?



Evaluation procedure of PIPs

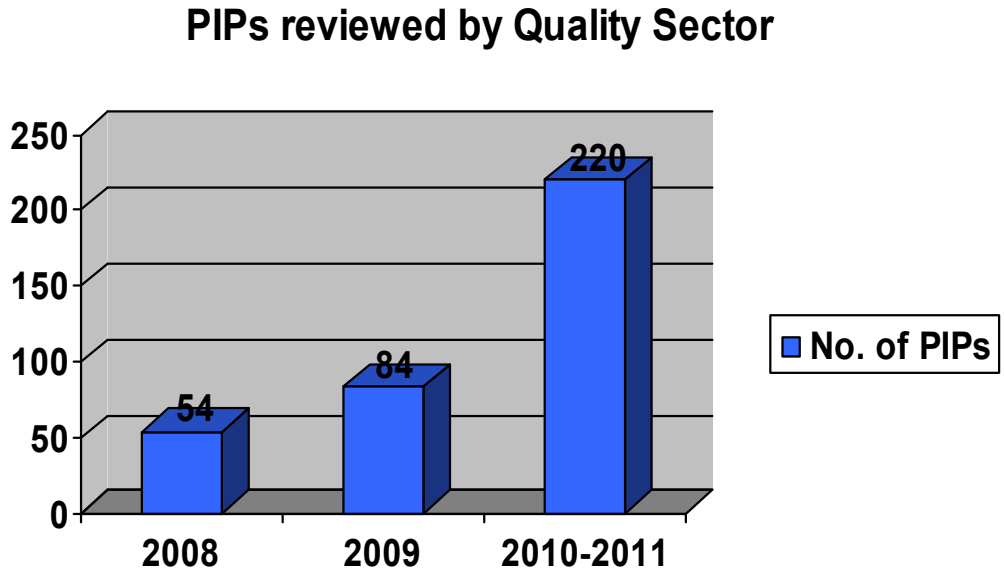
PDCO FWG Formulation Group – monthly meeting

- PDCO members (Chair: Dr Siri Wang) + external experts (hospital, academia).
- Discussion on formulation aspects and reporting to the PDCO.

PDCO Paediatric Committee - monthly meeting

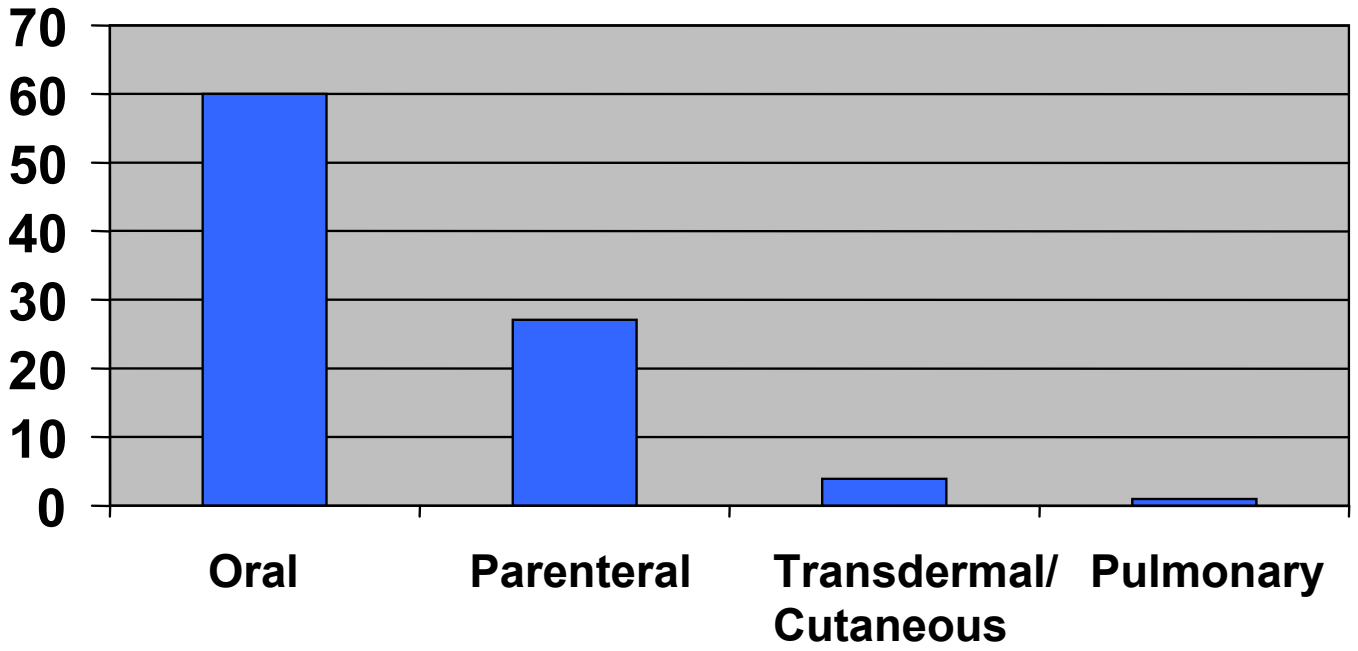
Applications assessed by FWG

Around 1000 PIPs- validated PIP/waiver applications (March 2011)



Classification according to Route of Administration –based on 2009 survey

(Caroline Bosc & Blanca Quijano)



30% of the oral formulations Acceptability, palatability, dosing….

http://pediatrics.aappublications.org/content/123/2/e235.full

Critical Points for Paediatric Formulations

- Route of administration
- Appropriate dosage forms
- **Excipients - 50% of the PIPs- choice excipient, safety, level, side effects……**
- Taste and palatability
- Delivery devices
- Rate of infusion
- Volume to be administered
- Wastage

How to select excipients

What do we know ? Guidelines, CHMP Opinion, Literature, Food Legislation…[1]

What are the concerns: reported cases (with patients) or potential risks ?

Absence of knowledge and tox data ?

1-Paediatric drug handling by Costello, Long, Wong, Tuleu, Yeung, Pharmaceutical Press 2-Toxic Additives in Medications for Preterm Infants Arch. Dis. Child. Fetal Neonatal Ed. published online 21 Jan 2009 by Whittaker, Mulla, Turner, Currie, Field and Pandya

How to select excipients 2

For instance when it comes to taste-masking agents & techniques, we ask ourselves…….[1]

- Flavours, sweeteners (i.e. aspartame, mannitol): analyse the side effects and the risks depending on the exposure

-Taste-masking techniques: consider coating (i.e. cellulose) or encapsulation (i.e. different kind of cyclodextrins with safety data) to avoid flavours

1 - Taste masking technologies in oral pharmaceuticals: recent development and approaches by Sohi H. et Al, Drug Development and Industrial Pharmacy, 2004, vol 30, n 5, 429-448

How to select excipients 3

Colorants- the questions we ask ourselves/points we keep in mind….

- Natural[1] or synthetic ? Composition known ?
- Colorants needed for the formulation or aesthetic purpose ?
- Synthetic azo-dyes are not recommended

1 - Natural colorants can present risks. The safety of pharmaceutical excipients by Pifferi G. and Restani P. Il Farmaco 58, 2003, 541-550

How to select excipients – key message

The overall approach is a risk benefit approach for each excipient depending on the condition, the age group, the exposure…etc…

This is **QUALITY** with regard to **SAFETY**

Case 1 – Preservatives & eye drops

Formulation issue:

Eye drops for the treatment of an orphan disease

Long term treatment (patients $\geq$ 4 years)

Can we accept the composition ?

Case 1 – continues

Discussion: Boric acid and sodium borate used as buffer only (and not as antimicrobial preservative - common in eye drops). Higher concentration compared to similar product- risk of irritation and safety issues.

Conclusion: After request for clarification, the applicant justified the concentration for the buffer, and provided some literature reference and comparison with existing products. The justification was accepted.

Case 2 – Sweeteners & flavours

Formulation: Oral solution for treatment of pneumonia and complicated infections (from birth onwards)

The applicant does not intend to develop specific paediatric formulation (plans to use the authorised adult's one).

Can we accept the excipients?

Case 2 – continues

Discussion: Exact composition of used formulations unknown.

+ 3 sweeteners (sucrose, mannitol and aspartam)

+ several flavours

Does the applicant plan to use all of them ?

Conclusion: The applicant was asked to reduce/clarify number of sweeteners and flavours. Rationale provided. Specific area + taste-masking can be difficult. Simple formulations better but if no major safety we cannot block "multi" sweeteners or flavours.

Case 3 – Colorants

Formulation issue:

Film-coated tablets

HIV indication-Long term treatment (above 12 years of age)

Colorants used in the formulation (Opadry II)- Is it an issue ?

Case 3 – continues

Discussion: Standard excipients- Lactose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate and magnesium stearate.

Film-coating (Opadry II): contains indigo carmine, titanium dioxide, yellow iron oxide. No azo dye. Already accepted by the PDCO.

Indigo carmine- Final report from the EC. Acceptable Daily Intake (ADI)= 5 mg/kg, children under 3 years old.

Conclusion: The formulation used in adolescents, the proposed formulation and coating can be accepted.

Case 4- Excipients and accuracy of dosing

Formulation issue:

IV Solution for injection or infusion

Anticoagulant agent for short-term use (from neonates onwards)

Same formulation used in adults will be used in paediatrics.

Case 4 - continues

Discussion:

No major issues regarding the composition (sodium hydroxide; mannitol and 5% glucose for injection or 0.9% sodium chloride). Mannitol is present but used for a short period, the quantity (0.5 mg/ml) is very low.

Conclusion: The applicant was asked to

discuss and monitor possible diuretic effect in neonates due to mannitol.

discuss the volume administered in the different age groups, the accuracy and feasibility of measuring those volumes.

An appropriate smaller vial should be considered for low weight neonates

Case 5- Formulation issue and acceptability

Formulation issue:

Hard capsules

Oncology treatment for long term use (above 5 years old)

Issues raised regarding the capsules ? The possibility of an IV formulation ?

Case 5-continues

Discussion:

Size of the capsules were discussed. Sizes 1 and 3 should be acceptable. However the acceptability to be demonstrated during the clinical trial with target population (+ the AS is toxic and the capsules cannot be opened).

The *iv* formulation was not mentioned anymore by the applicant. They stated that the *iv* formulation had limited activity in the clinical trial

Conclusion: The PDCO FWG concluded:

The size of the capsules for the age group should be fine but to be demonstrated during the clinical trials.

Further justification for not developing the *iv* formulation requested

Case 6 - Composition and device

Formulation issue:

Solution for injection

Hypotension treatment- paediatric intensive care- for short-term (very low gestational age newborn)

Issues were focussed on the composition of the formulation and the dosing of the product

Case 6- continues

Discussion PDCO FWG : Sodium metabisulphite- potential toxicity. ADI 3.5 mg/kg body-weight (oral administration). The proposed IV formulation and the amount of 5 mg/kg/24h was not accepted (above ADI). Also very precise administration pumps are required.

Conclusion: The PDCO FWG asked

To justify the high content of sodium metabisulphate and replace it by another antioxidant with a better safety profile if possible.

The proposed strength was accepted provided that appropriate dosing device is used (0.01 ml/hour).

Case 7 (BIO) Medical Device – dose accuracy I

Formulation issue:

Human insulin

Long term therapy

Group of age: Above 1 year

Case 7 - continues

Discussion:

The main concern raised during the discussion was in relation to the capability of the medical device (pen) to measure and deliver 0.5 unit dose for small children population (from 1 to 5 years old).

Medical device by the applicant only allows 1 unit dose.

Conclusion: In view of the very long half-life of the product, a **pen** with **0.5U increments** to be developed by the applicant and an investigation of a **lower concentration** or a **smaller vial** to decrease the wastage have been requested.

Case 8 (BIO) Medical Device – dose accuracy

Formulation issue:

Plasma factor in combination with human albumin.

Prevention of chemotherapy-induced neutropenia.

Group of age: Above 2 years.

Device: Prefilled syringe (PFS).

Case 8 - continues

Discussion:

Composition of formulation was acceptable.

Proposed paediatric administration: To transfer the content of the prefilled syringe into a more appropriate syringe for accurate dosing ➡ PFS not appropriate for smaller children.

Conclusion: The PDCO FWG requested to either **graduate the PFS** or to develop a **vial presentation** or propose an **appropriate device** to deliver the product for paediatric population in order to avoid the need for any transfer procedure.

Conclusion

- Apply:
  - The Precautionary principle
  - Benefit/Risk arguments

- Excipients – essential need for research and collaboration (i.e on-going projects, Database EuPFI, Initiative on excipients neonates….etc.)

Thank you for your attention. Any question?