EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Legislation and Available Guidance for the Evaluation of PIPs (Quality)

Viewpoint from the EMA

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Objectives

- To summarise the legal/regulatory context concerning the evaluation of ‘Quality’ aspects
- Existing guidance – is it relevant?
- To present the challenges and issues in relation to the current guidance
- To open the discussion

Legal basis

Council Regulation 1901/2006/EC of the European Parliament and of the Council on medicinal products for paediatric use amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 came into effect on **26 January 2007**.

http://www.emea.europa.eu/htms/human/paediatrics/regulation.html

Legal basis- continued

Concerning the PIP (Chapter 3, Section I, Article 15.2):

"…The PIP shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned.

In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population…."

Legal basis- The Spirit of the legislation

- 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.
- i.e. the spirit is not to place the preparation of paediatric medicines in a context which is ad hoc, extemporaneous, or magistral

Quality Evaluation in the Context of a PIP

- Not the same as the evaluation of the Quality of a medicinal product in the context of a Marketing Authorisation.

- Emphasis is on the *soundness* of the formulation for the specific population in question, at a high level. i.e. Is the formulation justified? Is it age-appropriate ? Rather than to pursue small points of detail e.g. the tightening of specifications, etc.

- Emphasis is very much on **Quality in relation to Safety**. If there is doubt concerning the safety profile of an excipient in paediatric use, it should probably not be accepted – We have to talk to our safety experts !

- Excipients which are safe for adult use may not be acceptable for paediatric use.

Quality evaluation

- Ideally should lead to

  relevant and acceptable safe formulations, which have convenient and precise dosing characteristics for the intended population, made on an industrial scale suitable for marketing.

Legal / Regulatory references

Food directive legislation (non exhaustive)

Directive 2006/52/EC (food additives)
Directive 94/35/EC (sweeteners)
Directive 94/36/EC (colourants)
Directive 2009/35/EC (colourants in medicines)

(Food legislation now takes precedence over old pharmaceuticals legislation on colouring matter in medicines).

Guideline on the format and content of applications for agreement of modification of a PIP (2008/C243/01)

http://www.ema.europa.eu/htms/human/paediatrics/pips.htm(PIP format)
http://www.ema.europa.eu/htms/human/paediatrics/sci_gui.htm(guidelines)

Guidance

The point of departure:

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

(Draft) QWP Guideline on paediatric formulations (on-going)

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

Guidance

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

- containing some specific Quality guidance since there was no Quality Guideline at that time
- formulation aspects for neonates

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

Guidance

Formulations of choice for the paediatric population *(EMEA/CHMP/PEG/194810/2005).*

the point of departure at the present moment

- Written by EU Experts / Academia /Industry /EMA
- Takes into account physiological and physicochemical issues that could be considered.
- Generally Well-received
- US NIH/NICHD Like it
- EFPIA : It's OK but it doesn't specify the "regulatory requirements".
- NB: A Reflection Paper - Not a regulatory guideline

Guidance

ICH Q8 'Note for Guidance on Pharmaceutical Development'
(CHMP/ICH/167068/04)

- This guidance is the overarching guideline on pharmaceutical development. It describes the data requirements for Module 3 of the dossier for a Marketing Authorisation in the EU
- Very general – not specifically focussed on paediatric formulations or PIPs
- Good formulation science is a very broad field - is a specific paediatric focus really necessary? Current consensus – yes.

Guidance

Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product' *(CHMP/QWP/396951/06)*

•A key guideline on the quality of excipients, Came into effect January 2008 …..

•*"…Excipients to be used in formulations for the paediatric population should be selected with special care. Possible sensitivities of the different age groups should be taken into consideration. For example, colouring agents with documented safety risks, e.g. azo dyes and other synthetic colouring agents, should not be used in medicinal products for paediatric use when only intended for aesthetic purposes…"*

•This guideline is not intended to highlight safety issues concerning the use of certain specific excipients, and should not be confused with a separate Commission guideline on safety warnings relating to specific excipients-→

Guidance

'Excipients in the Label and Package leaflet of Medicinal Products for Human Use' *(Eudralex 3BC7A).*

- Acknowledges that some excipients are not entirely inert – some have side effects . Here we see that excipients and formulations can indeed give rise to concerns and present a safety problem. Acknowledges that excipients should be kept to a minimum, even the so-called 'safe' excipients,
- Probably one of the most relevant guidelines in the context of quality related to safety, BUT…
- Established safety profiles & warning statements are based mostly on data in adults, and apply to the adult population

(cont'd)

- It is not the main objective of Eud 3BC7A to contra-indicate certain excipients in the development of medicines
- It seems to take the position that the formulation is a 'given' and provides very little advice concerning the *a priori* choice and justification of excipients in pharmaceutical development. It is applied in an *a posteriori* sense, giving advice at the end, i.e labelling and package leaflet information for the patient.
- Now a little out of date – What is needed?
- A revision to include more warnings relevant to paediatric patients ?..or a New guideline focussing on paediatric patients?

Guidance

Opinions and reports for specific substances published by the European Food Safety Agency (EFSA)

- When developing or evaluating PIP formulations, these reports may be consulted , especially for oral products, BUT…
- Safety profiles and warning statements seem to be based mostly on data relating to adults, although some toxicology studies may be relevant to paediatric population.

Evaluation procedure of PIPs

PDCO FWG Formulation Group – monthly meeting

- PDCO members (Chair: Dr Siri Wang) + external experts (hospital, academia…)
- Discussion and reporting to the PDCO. Focus is on ‘what are we going to ask the company to do?’

PDCO Paediatric Committee - monthly meeting

Remaining Issues

- Need for further guidance ?
- Need for more relevant safety data on established excipients ?
- More Team work necessary ?:

Regulators ⟺ Academia ⟺ Industry

Quality Experts ⟺ Safety Experts

Thank you for your attention. Any questions?