Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Examples of guidance documents by health authorities and institutional bodies on neonatal formulations

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Description	This tools lists examples of documents published by regulatory authorities and institutional bodies concerning neonatal formulations
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Formulations, Regulations

Authors: Beate Aurich, Valéry Elie,
Naura Mahmoudi, Evelyne Jacqz-Aigrain

Disclaimer: **Sponsors and researchers unfamiliar with clinical trials in neonates and/or neonatology are advised to seek expert advice due the complexity of neonatology.**

Correspondence email: pedcrin@ecrin.org

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Introduction

Medicines prescribed to neonates need to have a favourable benefit-risk balance including a formulation adapted to the neonatal population which, for example, limits the risk of medication errors and does not contain excipients which are known to be harmful.[1] Neonatal formulation development is challenging due to rapid maturational changes which may influence pharmacokinetics (PK) and/ or pharmacodynamics (PD), a heterogeneous patient population, common polypharmacy; as well as limits on fluid volume, flow rate of administration, excipients considered to be safe and route of administration.[2-7] An additional challenge is that the formulation may need to be manipulated to suit neonatal dosing requirements, which may increase the risk of medication errors, lack of efficacy and toxicity.[2,8,9]

Formulation and excipients in neonates: Examples of documents published by regulatory authorities and institutional bodies

Regulatory authorities such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have published guidelines on formulation development and excipients including for neonates. Other institutional bodies such as the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) and the World Health Organisation (WHO) have published more general guidance. Examples of documents relating to neonatal formulations and published by regulatory authorities and institutional bodies are provided in Table 1.

Conclusions

Medicines used for treating neonates should have an age appropriate formulation to ensure safe prescription, preparation and administration and only include excipients which are tolerated by neonates. Researchers are advised to seek expert advice if a medicine needs to be adapted for the neonatal population in order to ensure best practice is used for its preparation and that an effective and safe dose is administered.

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Competing interests

All authors consider not having any competing interests for this tool. BA has worked for GlaxoSmithKline between October 2006 and September 2009 and holds company shares. Between October 2009 and May 2015 she has worked for Novartis.

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Table 1. Formulations and excipients in neonates: Examples of documents published by regulatory authorities and institutional bodies (not exhaustive)

Main topic (General guidance, formulation, excipients)	Title	Organisation	Reference
Formulation	Reflection paper: Formulations of choice for the paediatric population.	EMA	1
	Guideline on pharmaceutical development of medicines for paediatric use.	EMA	2
	Development of paediatric medicines: points to consider in formulation,	WHO	3
Excipients	Excipients in the labelling and package leaflet of medicinal products for human use	EMA	4
	Questions and answers on ethanol in the context of the revision of the guideline on "Excipients in the label and package leaflet of medicinal products for human use	EMA	5
	Questions and answers on propylene glycol used as an excipient in medicinal products for human use	EMA	6
	Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use.	EMA	7
General guidance	Guideline on the investigation of medicinal products in the term and preterm neonate	EMA	8
	General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry.	FDA	9
	Clinical investigation of medicinal products in the pediatric population E11	ICH	10
	Addendum to ICH E11: Clinical investigation of medicinal products in the pediatric population E11 (R1)	ICH	11

EMA= European Medicines Agency; FDA= Food and Drug Administration; ICH= International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use; WHO= World Health Organisation

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