



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

c B G
M E B

Paediatric formulations

GL on the pharmaceutical development of medicines for paediatric use

EMA SME workshop: Focus on quality for medicines containing chemical substances
London 4 April, 2014

Presented by: Diana van Riet-Nales

Senior Assessor, Medicines Evaluation Board in the Netherlands

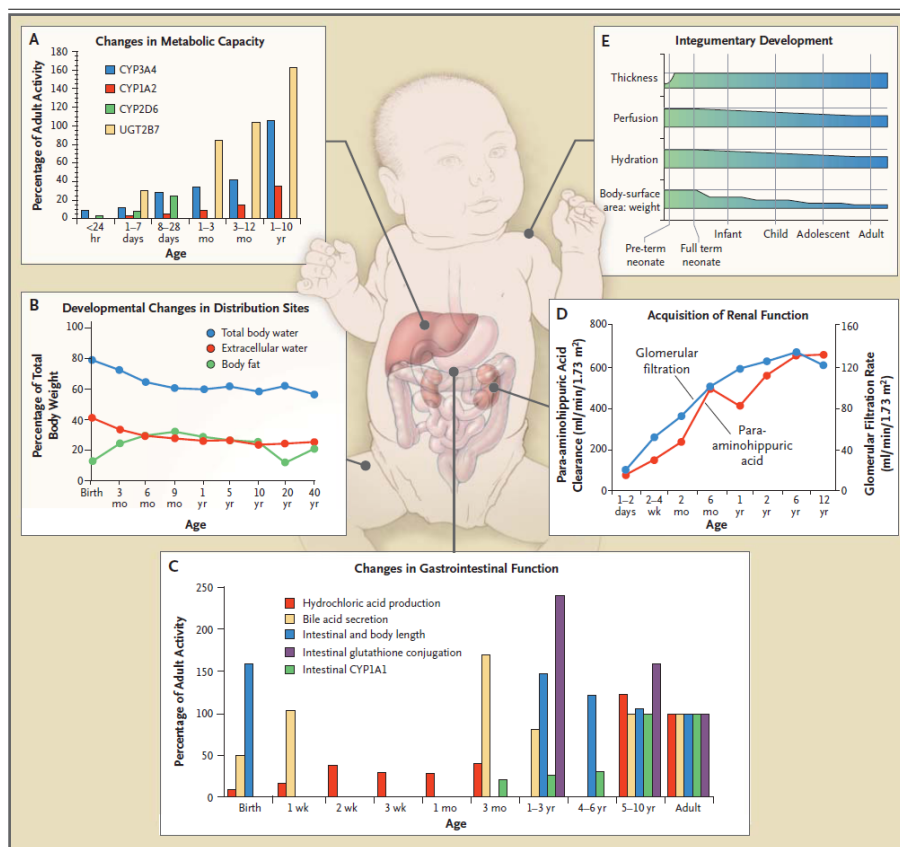
An agency of the European Union





Why children require special attention

children are no small adults





Why children require special attention

use of unlicensed/off-label medicines in children is/was widespread

Table III. Extent of unlicensed and off-label drug prescriptions in children in various countries and settings

Study	Country	Setting	Unlicensed and off-label drug prescriptions (%)	Patients receiving unlicensed and off-label drug prescriptions (%)
Turner et al. 1996 ^[7]	UK	PICU	31	70
McKenzie et al. 1997 ^[8]	US	A & E		34
Turner et al. 1998 ^[9]	UK	Inpatients	25	36
Turner et al. 1999 ^[10]	UK	Inpatients	35	48
Turner 1999 ^[11]	Australia	Inpatients	16	36
Conroy et al. 1999 ^[13]	UK	NICU	65	90
Wilton et al. 1999 ^[14]	UK	Community		22
Conroy et al. 2000 ^[12]	Europe	Inpatients	46	67
McIntyre et al. 2000 ^[15]	UK	Community	11	
Chalumeau et al. 2000 ^[16]	France	Community	33	56
Jong et al. 2000 ^[17]	The Netherlands	PICU	48	92

A & E = accident and emergency; **NICU** = neonatal intensive care unit; **PICU** = paediatric intensive care unit.



Why children require special attention

general lack of age-appropriate formulations

	Authorized medicines			Authorized active chemical entities		
	Paediatric medicines	All medicines for human use	Percentage paediatric vs. all medicines	Children	All chemical entities for human use	Percentage paediatric vs. all chemical entities
Route of administration (total)	3542	7410	48%	703†	1490†	47%
Oral	2247	4933	46%	357	726	49%
Parenteral	788	1439	55%	339	623	54%
Dermal	71	317	22%	23	144	16%
Ear/eye	52	190	27%	28	79	35%
Inhalation	138	170	81%	28	34	82%
Rectal	135	180	77%	20	47	43%
Nasal	101	127	80%	13	19	68%
Other	10	54	19%	15	39	38%
Oral dosage form (total)	2247	4933	46%	357†	726†	49%
Tablets	1422	3620	39%	237	592	40%
Capsules	334	633	53%	78	162	48%
Oral liquid preparations*	400	495	81%	133	167	80%
Powder/granules	65	93	70%	22	31	71%
Oral drops	11	17	65%	9	15	60%
Others	15	75	20%	9	44	20%

*Oral liquid preparations consisted of all medicines that are liquid when applied (e.g. effervescent tablets were also considered as oral liquid preparations).

†Some active chemical entities were available in more than a single dosage form.



Why children require special attention

general lack of appropriate formulations

	Authorized medicines			Authorized active chemical entities		
	Paediatric medicines	All medicines for human use ⁺	Percentage paediatric vs. all medicines	Paediatric medicines	All medicines for human use ⁺	Percentage paediatric vs. all chemical entities
Dermatologicals (D)	53	273	19%	17	83	20%
Cardiovascular system (C)	240	1267	19%	32	135	24%
Antineoplastic and immuno- modulating agents (L)	108	363	30%	39	127	31%
Sensory organs (S)	56	202	28%	30	86	35%
Musculoskeletal system (M)	212	413	51%	24	69	35%
Nervous system (N)	842	1660	51%	90	215	42%
Systemic hormonal preparations (H)	111	162	69%	22	42	52%
Blood and blood forming organs (B)	228	521	44%	106	174	62%
Alimentary tract and metabolism (A)	470	806	59%	106	170	62%
Anti-infectives for systemic use (J)	647	760	86%	147	185	79%
Respiratory system (R)	437	508	86%	84	96	88%
Antiparasitic products, insecticides and repellents (P)	40	45	89%	20	22	91%
Others (O)	72	173	42%	42	153	27%
Total*	3542		49%		1490	47%

*One chemical entity may relate to several ATC codes.



Industry did not solve problem by itself..

Paediatric Regulation (2007)

- lessons learned from earlier US incentives
- aim to improve health of children in Europe by
 - facilitating **development & availability** medicines 0-18 yr
 - ensuring medicines for children are **high quality**, ethically **researched** & authorised appropriately
 - improving availability **information on use** medicines for children
 - to be reached without subjecting children to unnecessary trials or delaying authorization of medicines for adults



Characteristics Paediatric Regulation

- system of **obligations & rewards** enforcing industry to consider children in clinical trials
 - new active substance, indication, route of administration
 - deferral or waiver may apply
- Paediatric Investigation Plan (**PIP**)
 - to be agreed by EMA PDCO
 - includes “binding” proposal paediatric formulation(s) for each subset paediatric population



Easy accessible additional information

an Medicines Agency - Human regulatory - Paediatric-medicine development - Windows Internet Explorer provided by CBG-MEB

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac05800240cd

ema.europa.eu

Home Find medicine **Human regulatory** Veterinary regulatory Committees News & events Partners & networks About us

Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
Scientific guidelines
Innovation Task Force
SME office
▼ Paediatric medicine
Background
Paediatric Regulation
Application guidance
Opinions and decisions
Post-assessment

► Home ► Human regulatory ► Paediatric medicine

Paediatric-medicine development

Email Print Help Share

The European Medicines Agency has a number of important tasks and responsibilities relating to the development of paediatric medicines. These were brought in by the Paediatric Regulation in January 2007.

This legislation concerns the development and authorisation of medicines for use in children aged up to 17 years and introduced sweeping changes into the regulatory environment for paediatric medicines, designed to better protect the health of children in the European Union (EU). The main change introduced was the creation and operation of the Paediatric Committee within the Agency to provide objective scientific opinions on development plans for medicines for use in children.

This section of the website provides information for companies or individuals wishing to develop a paediatric medicine and requiring guidance for the approval of a paediatric investigation plan (PIP), together with other information relating to paediatric medicines.

More information

- [Paediatric Regulation](#)
- [Application guidance](#)
- [Opinions and decisions on paediatric-investigation-plan applications](#)
- [Post-assessment guidance](#)
- [Supporting information](#)
- [Paediatrics: Regulatory and procedural guidance](#)

Related information

- [Opinions and decisions on paediatric investigation plans](#)
- [Paediatric Committee](#)
- [European Network of Paediatric Research at the European Medicines Agency \(Enpr-EMA\)](#)
- [Medicines for children: Background information](#)
- [Better medicines for children \(22/05/2013\)](#)

All Microsoft Office documents submitted to the European Medicines Agency must be in a format compatible with MS Office 2003, Office 2007 and Office 2010 formats cannot currently be accepted. PDF certified electronic application forms require Adobe Reader 10.0 or higher. Please visit [eSignature](#) for more information



Paediatric Regulation & formulations

Medicines Directive
2001/83

Paediatric Regulation
1901/2006/EC



which aspects are critical to children and which standards to apply (better as what? does a suboptimal taste qualify for a PSRPH?)



Approach to guideline development

- 2006 EMA reflection paper (discussion document)
- 2008 concept paper to guideline; annex incl. guiding principles
- multidisciplinary drafting group (PDCO, QWP, NCA, academia)
- 2015 guideline into operation
 - 1 guideline for PIPs, MA-applications/variations, innovator/generics
 - guideline applies prospectively, but industry should remind
Dir 2001/83 Annex 23 i.e. regulatory dossier should remain state of the art



Joint writing process with industry not possible

But

- EFPIA white paper prior to drafting process
- high focus on mutual information sharing as knowledge was scarce, but rapidly evolving (e.g. EUPFI conferences)
- input to public consultation highly appreciated (published)

Table II. Impact of pharmaceutical technologic aspects on patient-related outcomes parameters.^{24-28,31-119}
Data are number (%) of assessments.

Patient-Related Outcomes Parameter	Pharmaceutical Technologic Aspect			All Assessments (N = 176)*
	Formulation and Dosage Form (n = 85)	Route and Frequency of Administration (n = 77)	Packaging, Administration Device, and User Instruction (n = 14)	
Patient acceptance	38 (45)	5 (6)	1 (7)	44 (25)
Patient preference	19 (22)	4 (5)	0	23 (13)
Adherence	11 (13)	15 (19)	6 (43)	32 (18)
Clinical efficacy	8 (9)	31 (40)	2 (14)	41 (23)
Side effects and tolerability	8 (9)	22 (29)	0	30 (17)
Administration errors	1 (1)	0	5 (36)	6 (3)

*Two investigations assessed >1 pharmaceutical technologic aspect.



Guideline on pharmaceutical development of medicines for paediatric use

Table of contents

Executive summary	3
1. Introduction (background)	3
2. Scope.....	4
3. Legal basis.....	5
4. General considerations	5
5. Characteristics of the active substance	5
6. Route of administration and dosage form.....	6
6.1. General considerations.....	6
6.2. Oral administration.....	6
6.3. Nasal preparations	11
6.4. Preparations for inhalation.....	11
6.5. Rectal preparations.....	12
6.6. Cutaneous and transdermal preparations	12
6.7. Eye and ear preparations	12
6.8. Parenteral administration	13
6.9. Fixed dose combinations	14

7. Dosing frequency.....	14
8. Modified release preparations	14
9. Excipients in the formulation	14
9.1. General considerations.....	14
9.2. Colouring agents	18
9.3. Flavours	18
9.4. Preservatives	18
9.5. Sugars and sweeteners	18
10. Patient acceptability	19
11. Container closure system, measuring device, administration device and packaging	21
11.1. General considerations	21
11.2. Container size	22
11.3. Measuring device.....	22
11.4. Other devices.....	23
12. User information (summary of product characteristics and package leaflet)	23
Definitions	23



Route of administration and dosage form

tablets

- young children may swallow small tablets
tablet size versus age to be further confirmed
- crushing and/or mixing with food no alternative for real age-appropriate formulation
suitability any handlings to be confirmed
- tablets may be broken
suitability break mark to be demonstrated
within tablet content uniformity may be an issue



Route of administration and dosage form

oral liquid versus oral solid flexible dosage forms

- several forms may be requested for children of different ages and/or health conditions
- solid and liquid forms both acceptable, but clear justification needs to be provided (advantages/disadvantages different forms)



Excipients

- excipients may have different safety profile in adults & children e.g. ethanol, propyleneglycol
- use (type and maximum daily exposure) to be justified by **INDUSTRY** (not the assessor)
- guideline contains flow sheet with considerations how such justification can be established
- update of excipients guideline warranted (relates to any necessary warnings SmPC; not acceptability excipient in itself)



Patient Acceptability

- not to be understood as 100% in all relevant age groups
- integral part pharmaceutical development
- preferably studied in children as part of the clinical trials
- otherwise to be demonstrated by other means
- to be reconfirmed in case of variations
- industry may choose its own approach



Paediatric guideline & overviews

European Medicines Agency - Quality - Quality: Pharmaceutical development - Windows Internet Explorer provided by CBG-MEB Citri

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000362.jsp&mid=WC0b01ac0580028eb2

ema.europa.eu

Convertieren Selecteren

Favorieten FenFStart - Science - Utrec... Utrecht University - Pharma... WebUren - Agentschap CBG... http--www.ema.europa.eu... Web Slice-galerie

European Medicines Agen... Joint CHMP/CVMP/QWP Meet...

An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Text size: A A A Site-wide search GO

Search document library

Follow us: Twitter RSS

Home Find medicine **Human regulatory** Veterinary regulatory Committees News & events Partners & networks About us

Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
Scientific guidelines
Search guidelines
Quality
Active Substance
Manufacturing
Impurities

Home Human regulatory Scientific guidelines Quality Pharmaceutical development

Quality: Pharmaceutical development

Email Print Help Share

If you have comments on a document which is open for consultation, please use the [Form for submission of comments on scientific guidelines](#).

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Concept paper on the need for a reflection paper on quality aspects of medicines for older people	Concept paper	EMA/CHMP/QWP/70174/2013	Release for consultation April 2013		Deadline for comments 30 June 2013
Pharmaceutical development of medicines for paediatric use	Overview of comments Adopted guideline Draft guideline - Rev.1 Overview of comments Draft guideline	EMA/CHMP/QWP/805880/2012 Rev. 2	July 2013	15 February 2014	



**Thank you for your
attention!**