EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

cBG MEB

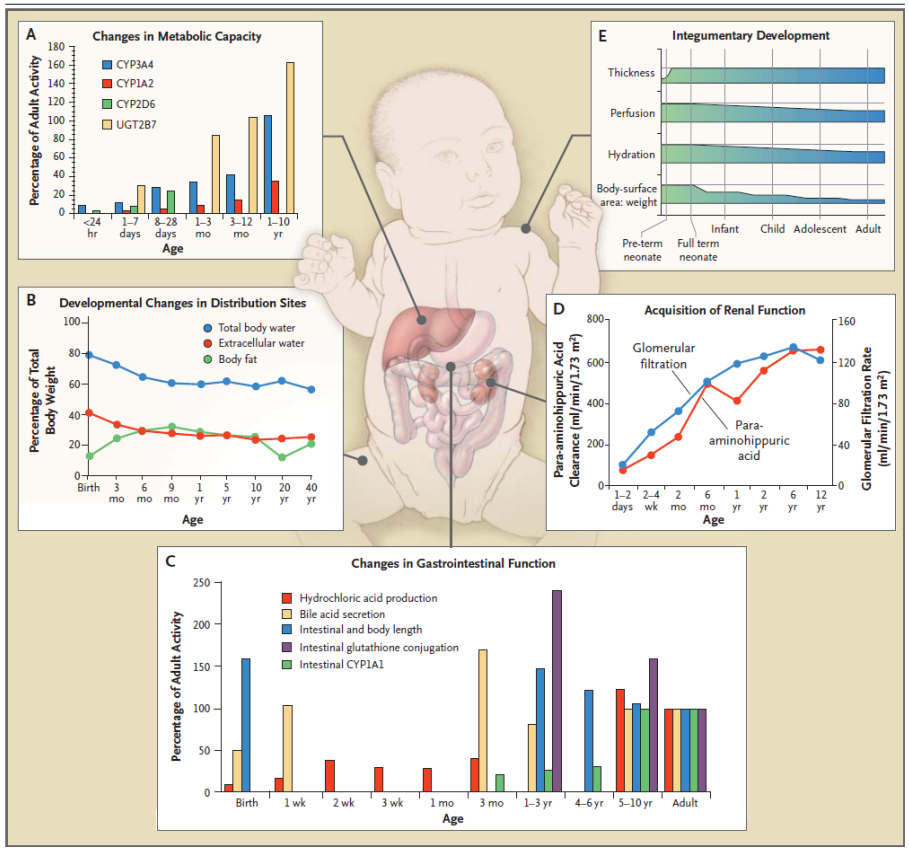
Paediatric formulations

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

Why children require special attention

children are no small adults



Kearns GL et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67.

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.

Choonara I. Conroy S. Unlicensed and off-label drug use in children. Drug Safety 2002. 25(1):1-5.

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.

van Riet-Nales DA, de Jager K, Schobben AFAM, Egberts TCG, Rademaker CMA. The availability and age-appropriateness of medicines authorised for children in the Netherlands. Br J Clin Pharmacol. 2011 Apr 8

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%
Muscoskeletal 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.

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Industry did not solve problem by itself..

Paediatric Regulation (2007)

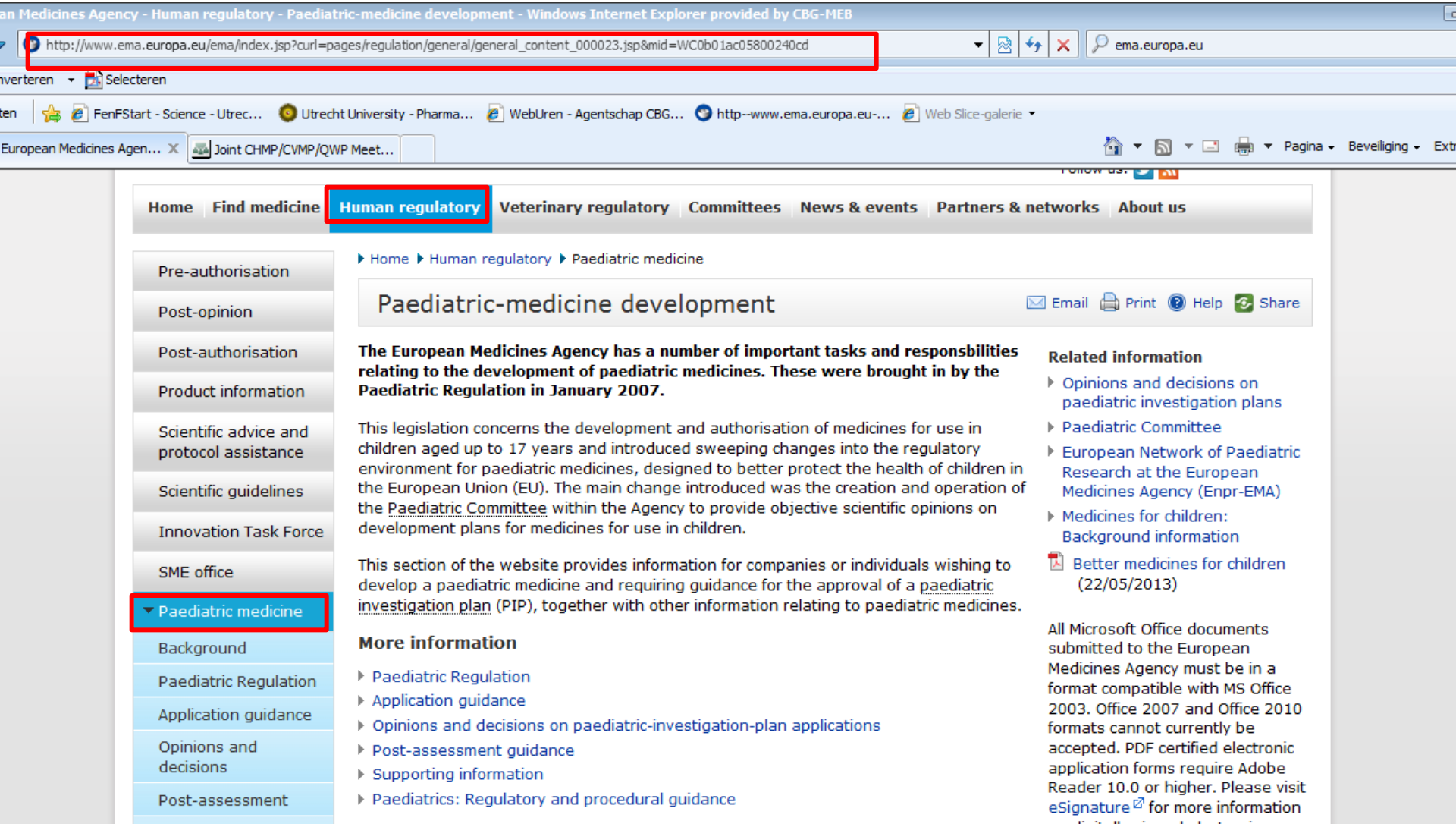
- lessons learned from earlier US incentives
- aim to improve health of children in Europe by
  - facilitating development & availability medicines 0-18 yr
  - ensuring medicines for children are high quality, ethically researched & authorised appropriately
  - improving availability information on use 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

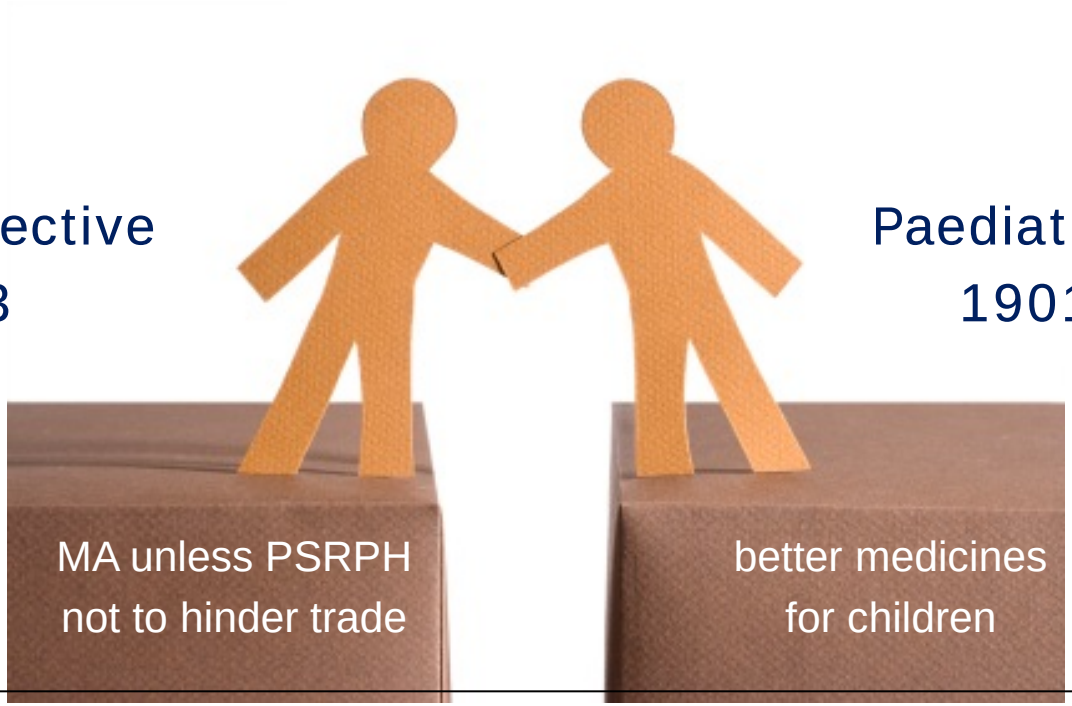
- Paediatric Investigation Plan (PIP)
  - to be agreed by EMA PDCO
  - includes “binding” proposal paediatric formulation(s) for each subset paediatric population

Easy accessible additional information



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

<u>But</u>

- 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: Formulation and Dosage Form (n = 85)	Route and Frequency of Administration (n = 77)	Packaging, Administration Device, and User Instruction (n = 14)	All Assessments (N = 176)*
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.

STEP database

Database of safety and toxicity of excipients for paediatrics

Guideline on pharmaceutical development of medicines for paediatric use

Table of contents

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf

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)

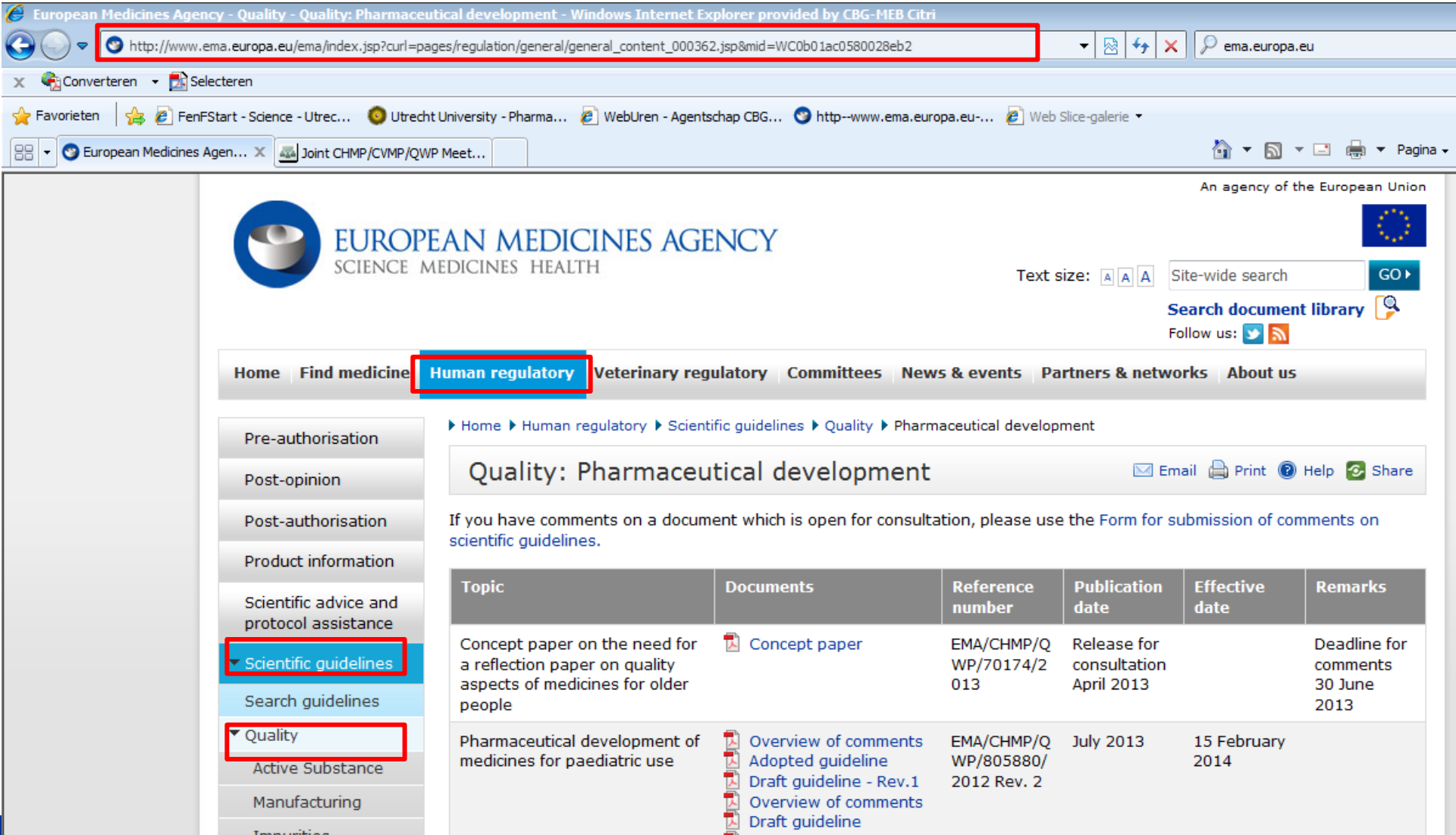
Excipients

- excipients may have different safety profile in adults & children e.g. ethanol, propyleneglycol
- use (type and maximum daily exposure) to be justified by INDUSTYRY (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



Thank you for your attention!

Diana van Riet - Nales l Medicines Evaluation Board in the Netherlands l da.v.riet@cbg-meb.nl