EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Organ Maturation Tables

Possibly identifying maturation related adverse drug reactions

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Paediatric Medicines

The Rationale

- Better use of Eudravigilance data for paediatric medicines.
- ADRs in adults and children are different (types, drugs).
- Differences may also be due to increased susceptibility to some ADRs because organs are still immature.
- Can we identify possible ADRs that are maturation related?

Methodology

- Identify key literature on OM (articles, book chapters, guidelines)
- Prepare OM table (specify maturation of key sub-functions, enzymes, main structures within organ)
- Send OM tables for Expert Review (experts in the field, PDCO,..)
- Finalize

Renal system maturation

Renal system Function / Age subsets	0 – 1 year	1 – 2 years	2 – 3 years	Up to 18 years
Glomerular filtration rate (GFR)	Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area increases more slowly to reach adult levels **between 1 to 2 years of age.**			
Tubular secretion	The renal tubular secretion capacity increases over the first months of life and then declines to reach the adult level (per unit of body area) at ~ **7 months to 1 year of age.** The organic anion pathway matures faster than the organic pathway.			
Tubular reabsorption	The development and maturation of the glomerular permeability functions and the renal tubular reabsorption are gradual and continuous processes from **birth** to **adolescence**. The key stage of their maturation is at ~ **1 and 3 years of age.**			

References:

1. Guideline on the investigation of medicinal products in the term and preterm neonate. CHMP and PDCO, EMEA, London 25 June 2009.

2. Paediatric Drug Development. Mulberg AE, Silber SA, Van den Anker JN. John Wiley & Sons, 2009.

Liver maturation

	Age (after birth) and maturation period / Hepato-biliary system and metabolic pathways	1 month	2 months	3 months	4 months	5 months	6 months	12 months	15 months	2 years	5 years
Phase I Enzymes	CYP3A4 (midazolam, itraconazole)										
	CYP1A2 (caffeine, theophylline)										
	CYP2D6 (dextromethorphan)										
	CYP2C9/CYP2C19 (benzodiazepines, proton pump inhibitors)										
	CYP2E1 (acetaminophen, halothane, ethanol)										
	FMO (chlorpromazine, promethazine)										
Phase II Enzymes	Glucuronidation UGT1A (acetaminophen)										
	Glucuronidation UGT2B (chloramphenicol, morphine)										
	Sulfation SULT1A1/SULT1A3 (acetaminophen; iodothyronines and catecholamines in foetus)										
	NAT2 (caffeine, isoniazid)										
	Bile flow (reaching up to the adult levels)										

Reference:
Mulberg AE, Silber SA, van den Anker JN; Paediatric Drug Development: Concepts and Applications; Developmental hepatic pharmacology in paediatrics; 2009; p. 243.

Brain maturation

Brain/brain elements	Period of maturation (postnatal months and years of age)	1 m	6 m	12 m	18 m	24 m	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y
Neural tube differentiation	Up to 1st month of age																					
Blood brain barrier	Until 6th month of age																					
Proliferation and organization of synapses	50% at 2 yrs; 100% at 4 yrs																					
Myelination	50 % of corpus callosum at 18 months; up to 20-30 yrs																					
Brain size	80% at 2 yrs; 90% at 5 yrs; remodelling of white and gray matter up to 20-30 yrs																					
Cortical gray matter maturation (motor & sensory systems, memory, audio-visual input, object recognition)	1. Frontal lobe: 11 yrs girls & 12.1 yrs boys 2.Temporal lobe: 16.7 yrs girls & 16.2 yrs boys 3. Parietal lobe: 10.2 years girls and 11.8 yrs boys																					
Subcortical gray matter maturation (control of movement and muscle tone, higher cognitive functions, attention, affective states)	Nucleus caudatus size peak: 7.5 yrs girls & 10.0 yrs boys																					
Amygdala and hippocampus maturation (emotion, language, memory)	Between 4 yrs and 18 years																					
White matter maturation	1. Lobar white matter volumes increase up to 30 years 2. Corpus callosum: between 4 yrs and 18 years (integrating left & right hemispheres; unification of sensory fields, memory storage and retrieval, attention & arousal, enhancing language and auditory functions)																					
Prefrontal cortex maturation	Up to the late adolescence – 17-18 yrs																					
Neurotransmitter system maturation (NMDA receptors)	Up to 3 years of age																					
Cholinergic and serotonergic systems	Through childhood and adolescence, in individuals possibly into adulthood																					

1. Volpe JJ, Neurology of the newborn, 5th ed., Elsevier Health Sciences, Philadelphia 2008, p5
2. Benes F, The development of the pre-frontal cortex, the maturation of neurotransmitter systems and their interactions, in: Handbook of developmental cognitive neuroscience (Nelson CA, Luciana M, eds) , MIT press, 2001

Lung maturation (under construction)

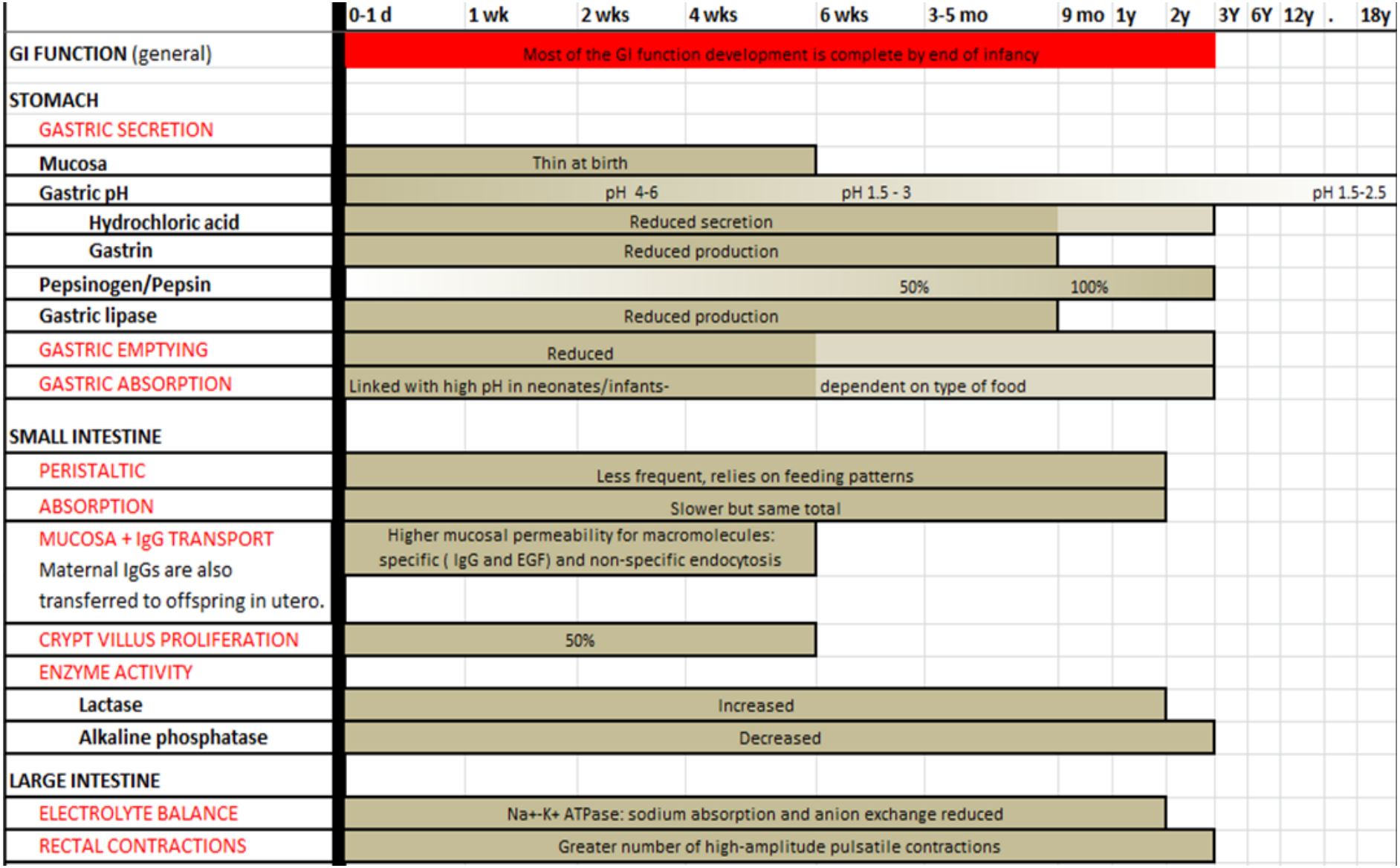
Development of the Pulmonary System

		Fertilization								Birth							
	Age subset	Embryogenesis		Foetal development						Neonate/ Infant	Child						
		0 w	5 w	10 w	15 w	20 w	25 w	20 w	35 w	40 w	1y	2y	3y	4y	5y	6y	7y	8y
Stage	Embryonic																	
	Pseudo-glandular																	
	Canalicular																	
	Saccular																	
	Alveolar (proliferation)																	
	Microvascular maturation																	
	Alveolar (expansion) (Normal lung growth period)																	

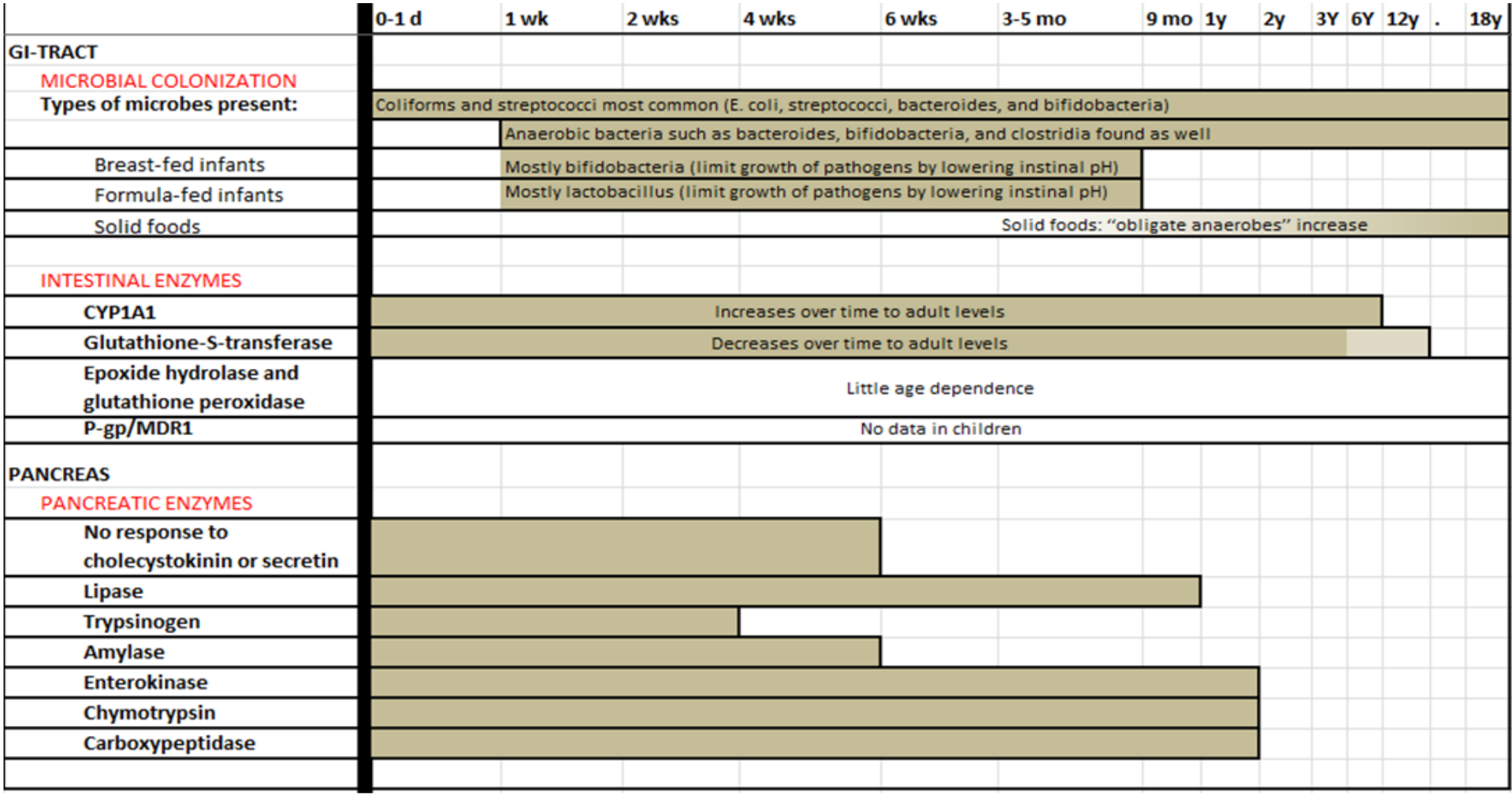
References:

- Zoetis T, Hurtt ME. Species comparison of lung development. Birth Defects Res B Dev Reprod Toxicol. 2003;68(2):121-4. Review.
- Zeltner TB, Burri PH. 1987. The postnatal development and growth of the human lung. II. Morphology Respirat Physiol 67:269–282.
- Burri PH. 1996. Structural aspects of prenatal and postnatal development and growth of the lung. In: McDonald JA, editor. Lung Growth and Development. New York: Marcel Dekker. p 1–35.
- Thurlbeck WM. 1975. Postnatal growth and development of the lung. Am Rev Respir Dis 111:803–844.
- Dietert RR, Etzel RA, Chen D, Halonen M, Holladay SD, Jarabek AM, Landreth K, Peden DB, Pinkerton K, Smialowicz RJ, Zoetis T. 2000. Workshop to Identify Critical Windows of Exposure for Children's Health: Immune and Respiratory Systems Work Group Summary. Environ Health Perspect 108(Suppl 3):483–490.

GI-system maturation (under construction)



GI-system maturation (under construction)



References:

- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Delopmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67. Review.
- Walthall K, Cappon GD, Hurtt ME, Zoetis T. Postnatal development of the gastrointestinal system: a species comparison.Birth Defects Res B Dev Reprod Toxicol. 2005 Apr;74(2):132-56.

The Application

Standard EudraVigilance Paediatric (SEVP) Query for *Drug X*

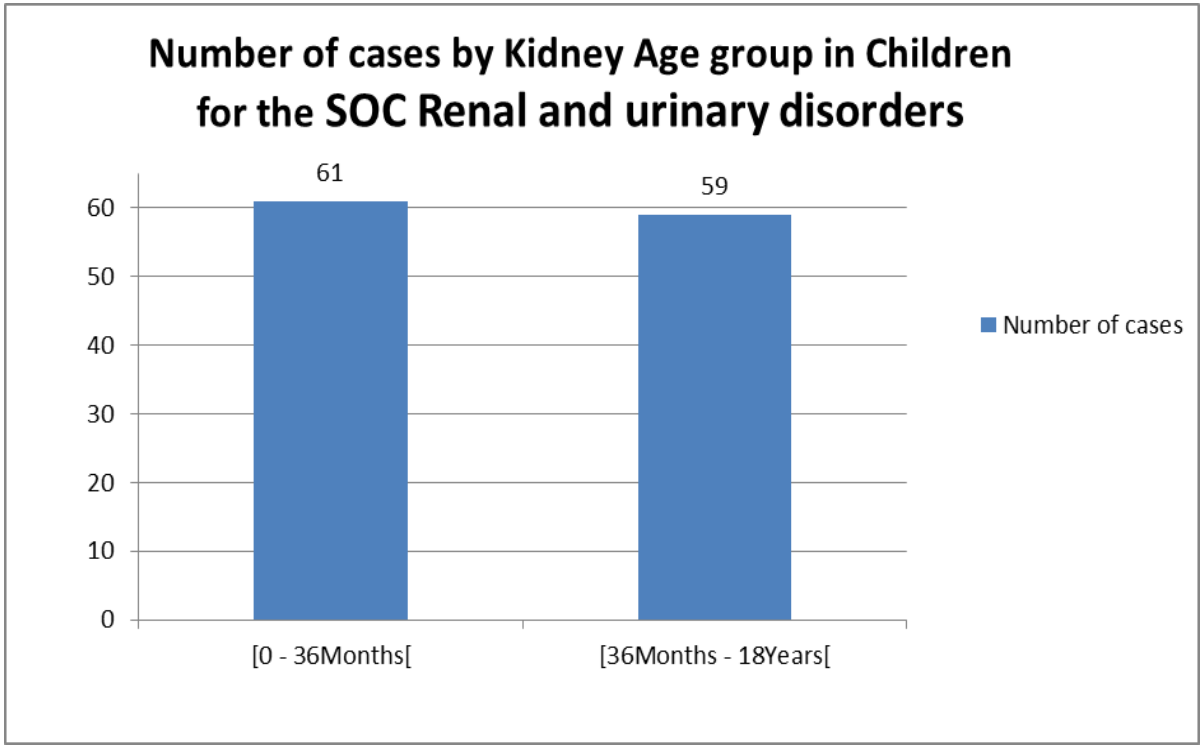
- PDCO concerns over potential renal toxicity in children *(Drug X)*
- Standard EV paediatric analysis was performed
- Paediatric age group analysis was performed also by kidney maturation stage (below and above 3 years).

Statistics children vs adult

Drug X	Paediatric cases	Ratio 1 Children vs. adult (95% CI)	Ratio 2 *Drug X* vs. other drugs in children (95% CI)	Ratio 3: *Drug X* vs. other drugs in adults (95% CI)
SOC 'Renal and urinary disorders'	120	3.13 (2.72-3.62)	14.91 (13.05-17.04)	2.66 (2.52-2.82)

Analysis of the specific paediatric issue

-> per the predefined age group categories taking into account the specific maturation of the kidney:



Conclusion

Information on organ maturation allows for:

- Better use of Eudravigilance data for paediatric medicines.
- Help identifying maturation related adverse drug reactions.