

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Working group "Psycho-Social Care from Fetus to Adult" of the Association for European Paediatric Cardiology (AEPIC)

Health and insurance aspects for CHD-patients in Europe

## Safer drugs for CHD-patients

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### USA 1938: Sulfanilamid Elixier and Diethylen glykol



Federal Food, Drug, and Cosmetic Act (FDCA)  
Quality assurance before market authorization of a new drug

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### Germany 1976



Drug approval for Quality, Safety and Efficacy

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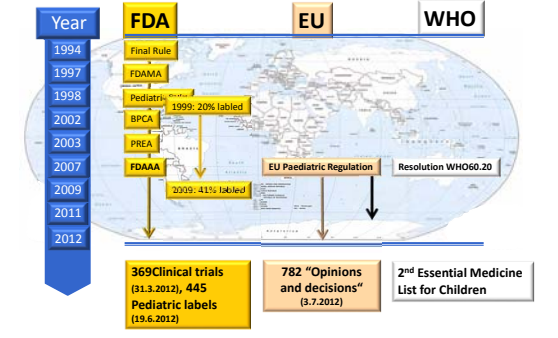
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## Drug development

- Quality
- Safety
- Efficacy

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### Drug development for children



Year	FDA	EU	WHO
1994	Final Rule		
1997	FDAMA		
1998	Pediatric		
2002	BPCA		
2003	PREA		
2007	FDAAA		
2009		EU Paediatric Regulation	
2011			Resolution WHO60.20
2012			

1999: 20% labelled  
2009: 41% labelled

369 Clinical trials (31.3.2012), 445 Pediatric labels (31.3.2012)

782 "Opinions and decisions" (3.7.2012)


2<sup>nd</sup> Essential Medicine List for Children

S. Lärer© <http://www.fda.gov/>; <http://www.ema.europa.eu/>; Sachs et al. 2012 JAMA 307 194-1915

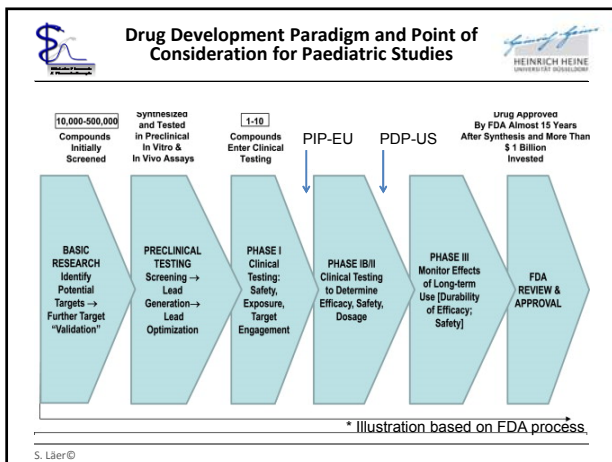
## Paediatric regulation EU

Improve health of children in Europe by:

- Facilitating development and availability of medicines
- Ensuring medicines for use in children are of high quality, ethically researched and authorised appropriately
- Improving availability of information on use of medicines



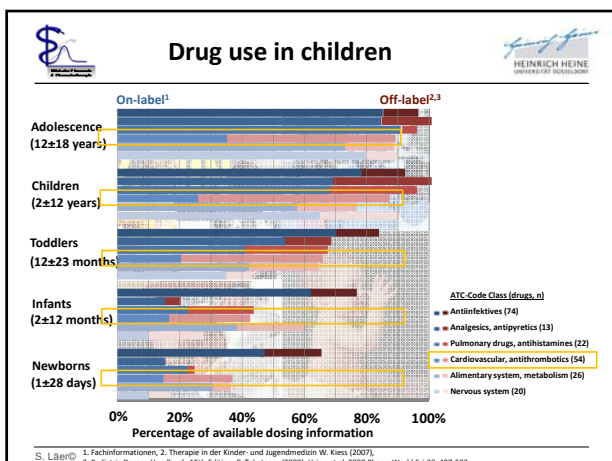
## Off-label use




## Definition

**Off-label Use**  
A use of the drug that is outside of its authorized product license as defined in the Summary of Product Characteristics (SmPC)

**Unlicensed Use**  
A use of a drug which is not licensed (in the country)



### Off-label use in Germany



- Children and adolescents in outpatients: about 15%**  
Mühlbauer et al (2009) Dtsch Arztebl Int 106:25-31
- In patients university clinic: about 30%**  
Hsien L et al. Pharm World Sci 2008; 30:497-502.
- Premature and neonates: 70%**  
Neubert et al (2010) Eur J Clin Pharmacol 66:87-95

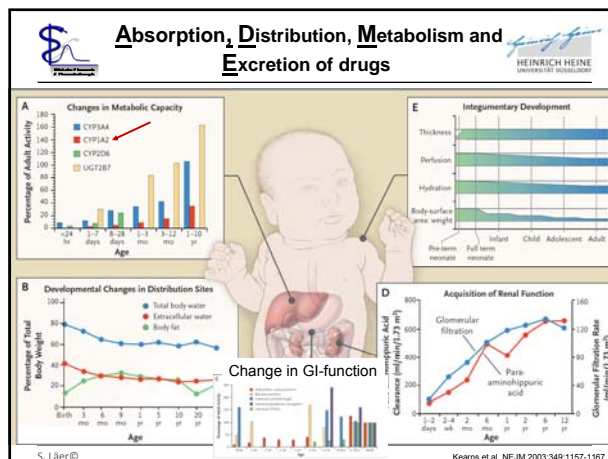
**Off-label use is higher in small and young patients**

### High unlicensed and off-label use of medicines in children in Europe

Country	Setting/population	Unlicensed and off-label		Reference
		of prescriptions	of children	
UK	Children's hospital	25 %	36 %	Turner et al 1998
UK, S, D, I, NL	Children's hospitals	46 %	67 %	Conroy et al 2000
UK	General practice	11 %	65 %	McIntyre et al 2000
F	Office based paediatr.	33 %	56 %	Chalumeau et al 2000
NL	Children's hospital	66 %	90 %	't Jong et al 2001
IR	District hospital ward	23 %	43 %	Craig et al 2001

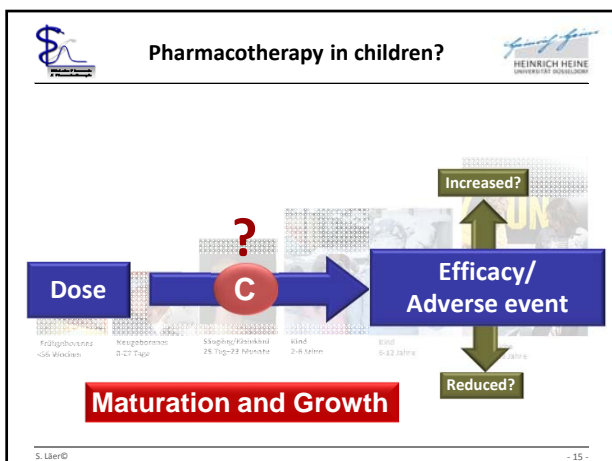
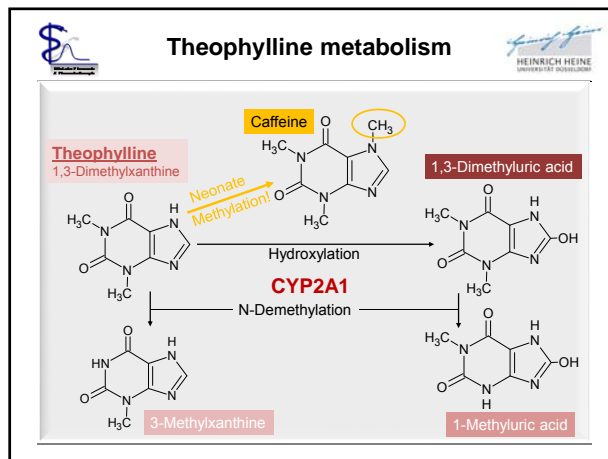
**Unlicensed** = Not licensed for children at all.  
**Off-label** = Prescribed outside the terms of the product license (not licensed for the age group, not licensed formulation, not licensed route of administration)

\* K. Hoopdu | 28.4.2011



### Off-label use - the problem

- Lack of age-related dosing guidelines
- Lack of age-related adverse effect profiles



### Is there a relation between off-label use and adverse events?

**Off-label use and adverse events**

	In patients	Out patients
Adverse events due to label use	3.9%	1.4%
Adverse events due to off-label use	6%	3.4%

Turner S et al. Acta Paediatr 1999; 88: 965-968  
Horen B, Br J Clin Pharmacol 2002; 54: 665-670

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**Enalapril Maleate**

- marketed in Europe since 1983
- prolonging survival in adult patients with hypertension, cardiac failure, and chronic renal disease
- first-line treatment for chronic heart failure (CHF) in children (European Medicines Agency Expert Group Meeting on Paediatric Heart Failure)
- only labelled for children >20 kg
- no licensed formulation suitable for children or for patients who cannot swallow a capsule or tablet in Europe: problems with chemical stability in solutions
- => included in the priority list for studies of off-patent paediatric medicinal products for CHF, hypertension, and chronic renal disease (EMA 2012).

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**Heart failure in children**

**Absorption, distribution, metabolism and elimination of enalapril in adults: prodrug for enalaprilat**

Conversion rate ≈ 70%. T<sub>max</sub> 3-4 h

Intrarenal conversion to Enalaprilat

Renal excretion

Mostly bound to ACE, limits elimination

**Effect of maturation and growth for enalapril?**

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**Pediatric and adult heart failure: epidemiology and drug treatment**

Relative incidence of heart failure syndrome in children

Relative incidence of heart failure syndrome in adults

DCM Treatment extrapolated from adults

CHD: Reduced or normal systolic ventricular function

Legend:

- Rhythm disorder
- Dilated cardiomyopathy (DCM)
- Congenital heart disease (CHD)
- Hypertension
- Dilated cardiomyopathy (DCM)
- Valve disease
- Coronary artery disease

RCTs=Randomised Controlled Trials

Practice Guidelines for Management of Heart Failure in Children 2004 J Heart Lung Transplant 23:1313-1333 - 23 -

**Enalapril suspension – a problem for small children**



Enalapril [%]

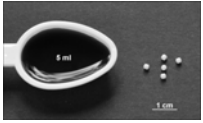
0 days, 2 days, 10 days, 43 days

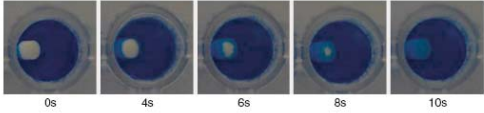
Legend: 5°C, 25°C, 40°C

MW ± s, n=3; ----- 90% stability limit



Martin Hermes, Dissertation Heinrich-Heine University Dusseldorf, 2012

 **Orodispersible mini-tablets** 

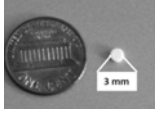





EU perspectives on paediatric formulations | Stoltenberg, G. Winzenburg, J. Breilkreutz, J. Appl. Ther. Res. 7: 141-146 (2005)

 **Oro-Dispensible-Mini-Tablets containing Enalapril Maleate** 

- Progress in pharmaceutical development of paediatric formulations – practical examples





**A real opportunity for children with heart failure**

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**Thank You!**

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