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Pharmacokinetic Peculiarities of Antimicrobial Treatment in Children and Neonates

Andreas H. Groll, M.D.

Infectious Disease Research Program
Center for Bone Marrow Transplantation and
Department of Pediatric Hematology/Oncology
University Children's Hospital Münster, Germany

Disclosures

- **Grants**
  - **Gilead, Merck, Sharp & Dohme, Pfizer**
- **Consultant**
  - **Amplyx, Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme and Schering-Plough**
- **Speakers' bureau**
  - **Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon**

Antibiotic Use Pediatrics

- **Relative to adults, children and adolescents are in general similarly vulnerable to infections**
- **However, differences exist as to**
  - **populations at risk**
  - **clinical presentation and epidemiology**
  - **validation and use of diagnostic procedures**
  - **pharmacology of antimicrobial agents**

Outline of Topics

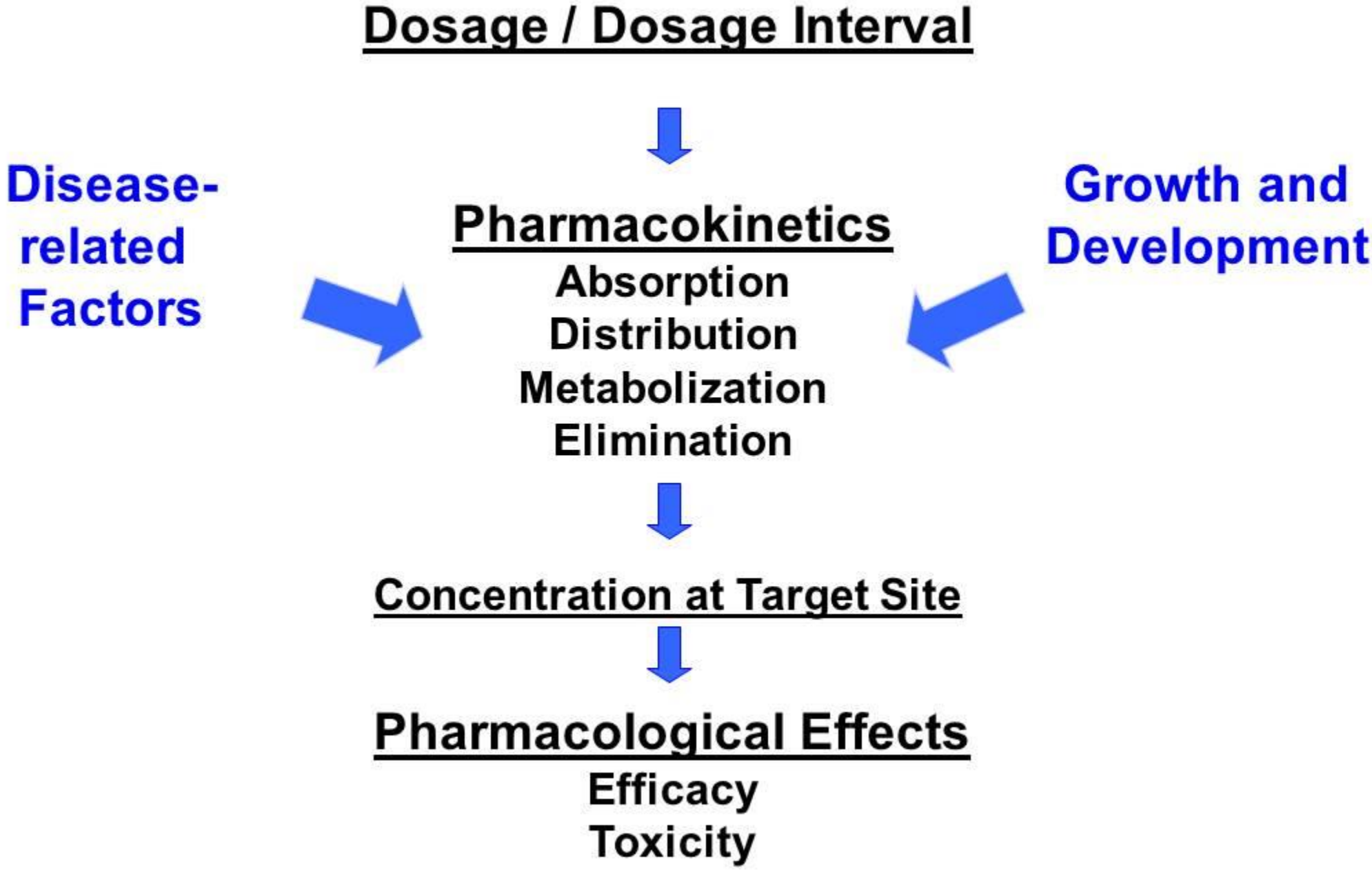
- **Overview on pediatric populations receiving treatment with antibiotics**
- **Principles of developmental pharmacology with examples from antimicrobial agents**
- **Regulatory concepts of pediatric drug development, achievements and challenges**

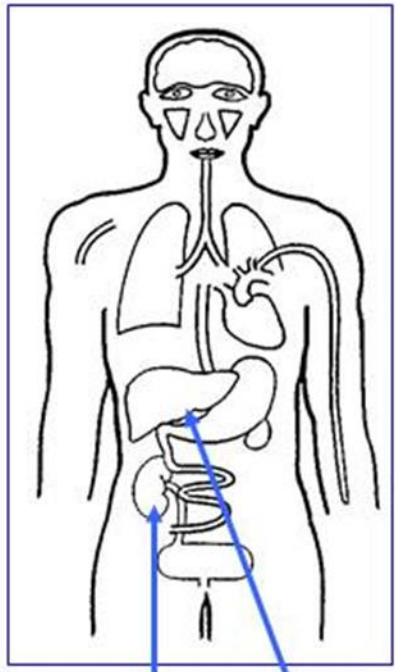
Populations Receiving Antibiotics

- **Large spectrum of conditions and comorbidities**
- **Large diversity of human physiology from intrauterine to adults status**

➢ **Challenge to appropriate drug treatment**

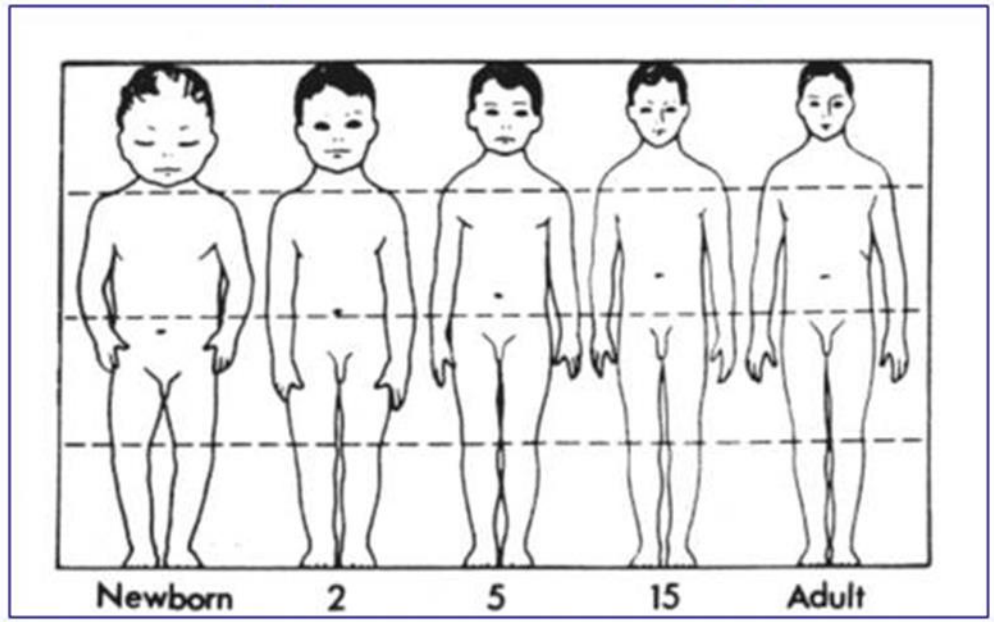
Principles of Developmental Pharmacology


Dosage / Dosage Interval
Disease-related Factors
Growth and Development
Pharmacokinetics
Absorption
Distribution
Metabolization
Elimination
Concentration at Target Site
Pharmacological Effects
Efficacy
Toxicity



Maturation processes
of excretory organs

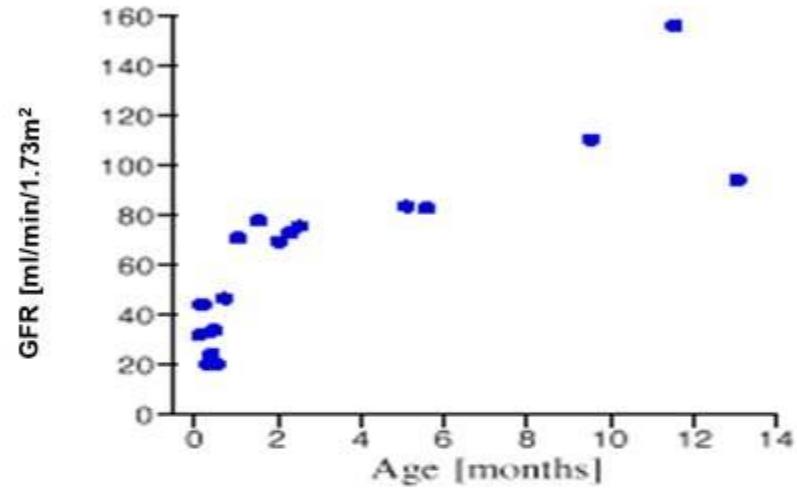
Changes in body mass and body composition



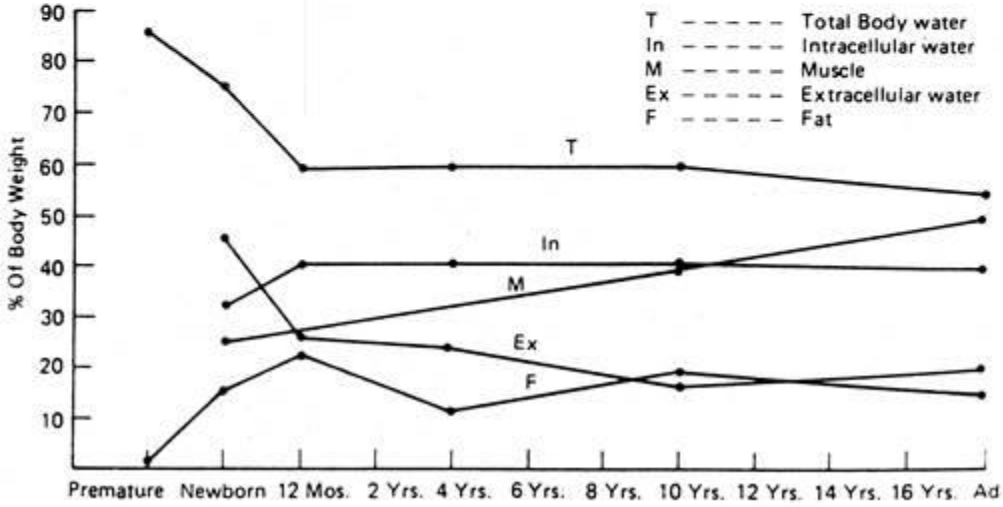
Scaling of dosing regimens based on body weight or body surface area generally inappropriate

Developmental Changes in Early Life

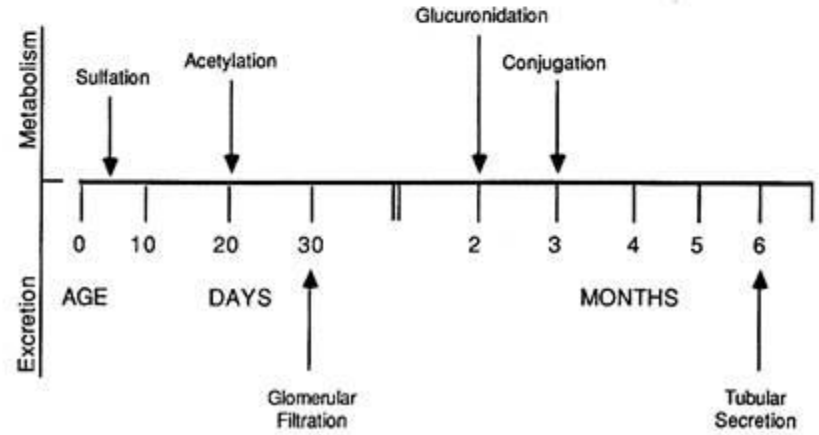
Glom. filtration rate:



% Body composition:



Hepatic functions:

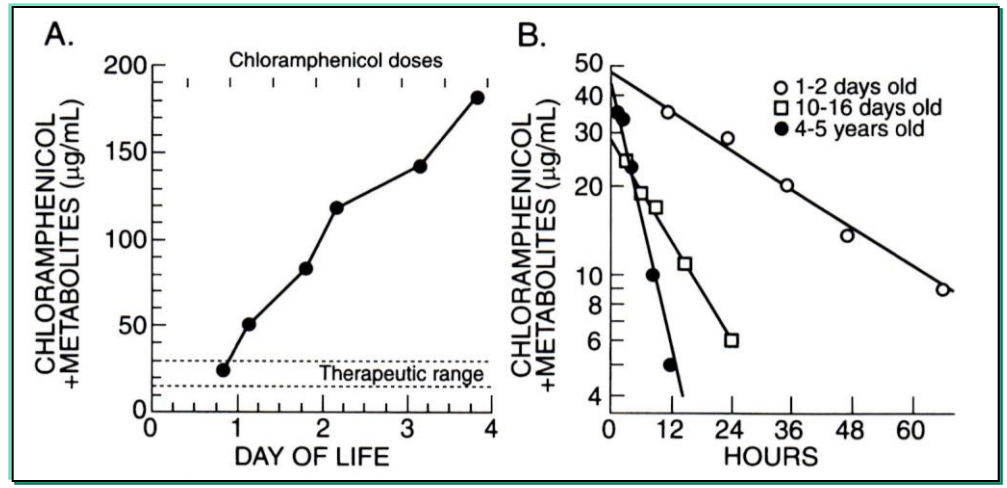


Developmental PK: Chloramphenicol and Hepatic Metabolism

Unexpected deaths in the late 1950s in newborns who had been treated with chloramphenicol *(grey baby syndrome)*

	All premature newborns		Good prognosis premature newborns (2001–2500 gm)	
	Number	Deaths	Number	Deaths
No empiric antibiotics	32	6	17	1
Penicillin + streptomycin[b]	33	6	24	0
Chloramphenicol[b]	30	19	16	8
Penicillin + streptomycin + chloramphenicol[b]	31	21	15	6

[a] Reproduced with permission from Burns LE, et al. N Engl J Med 1959;261:1318–21.



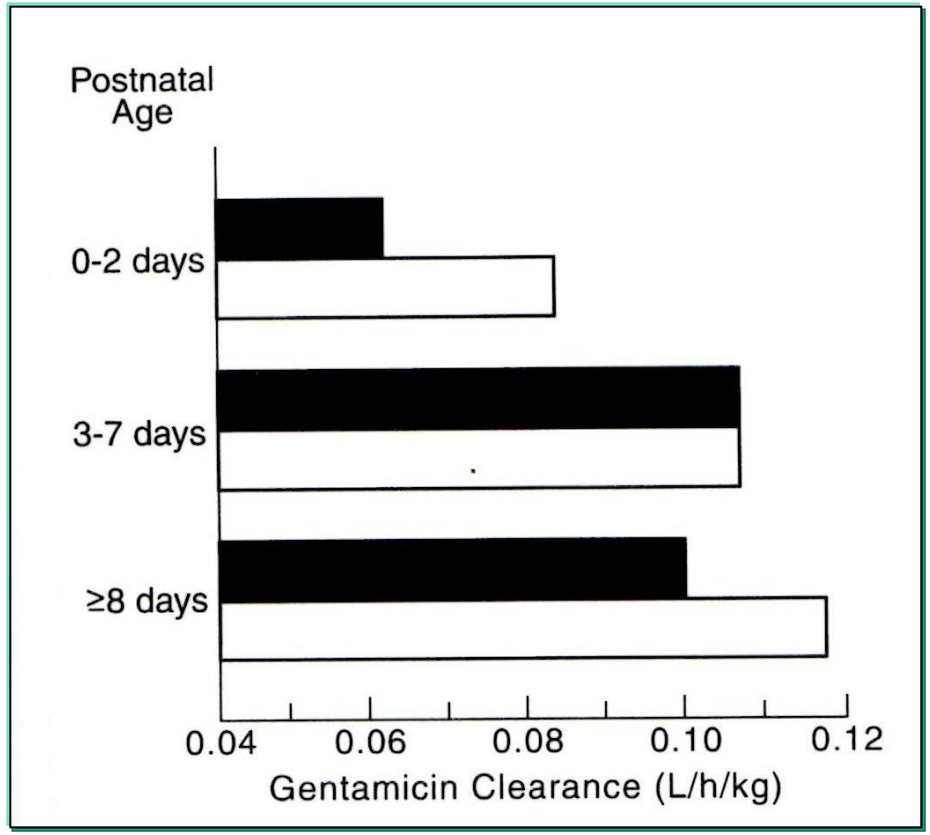
- **Chloramphenicol detoxified in the liver primarily by glucoronidation**
- **Dosing based on scaling of recommended doses in adults led to increased mortality through accumulation of drug & metabolites**

Burns et al. NEJM 1959: Weiss et al. NEJM 1960

Developmental PK: Gentamicin and Renal Clearance

Age-dependent plasma clearance of gentamicin in *premature* and *full term* newborns

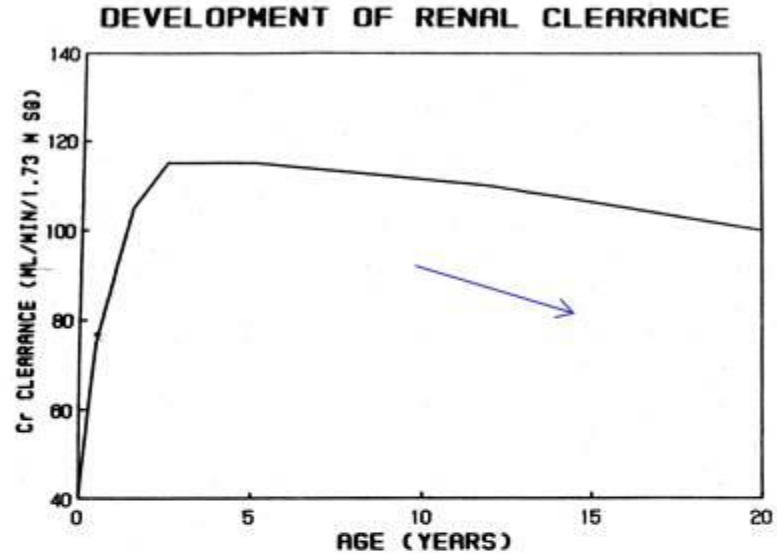
- **Antibiotic doses need frequently be increased after first 7 days of life**



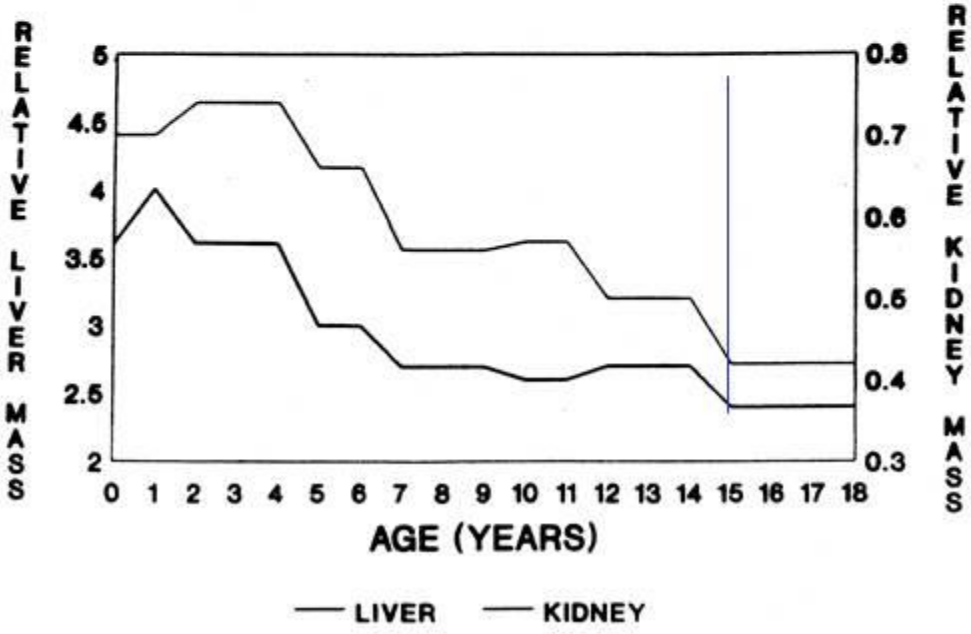
Pons et al. Ther Drug Monit 1988

Developmental Changes in Infancy / Adolescence

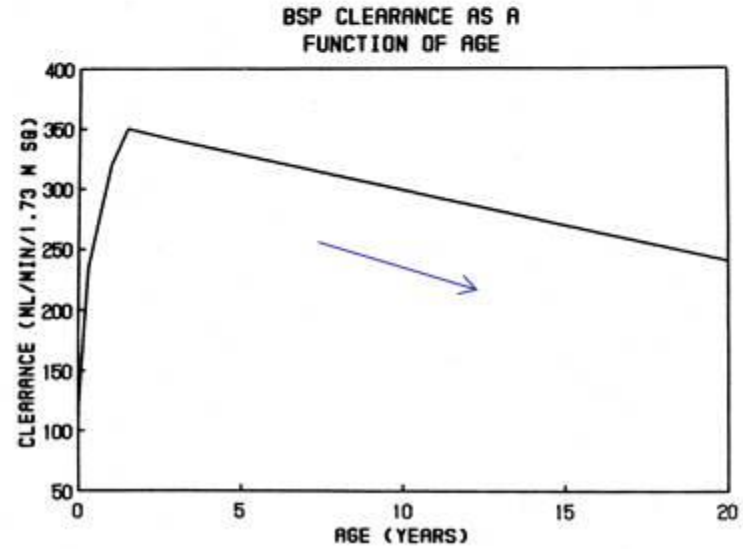
Glom. filtration rate:



% liver / kidney mass:



Hepatic function:

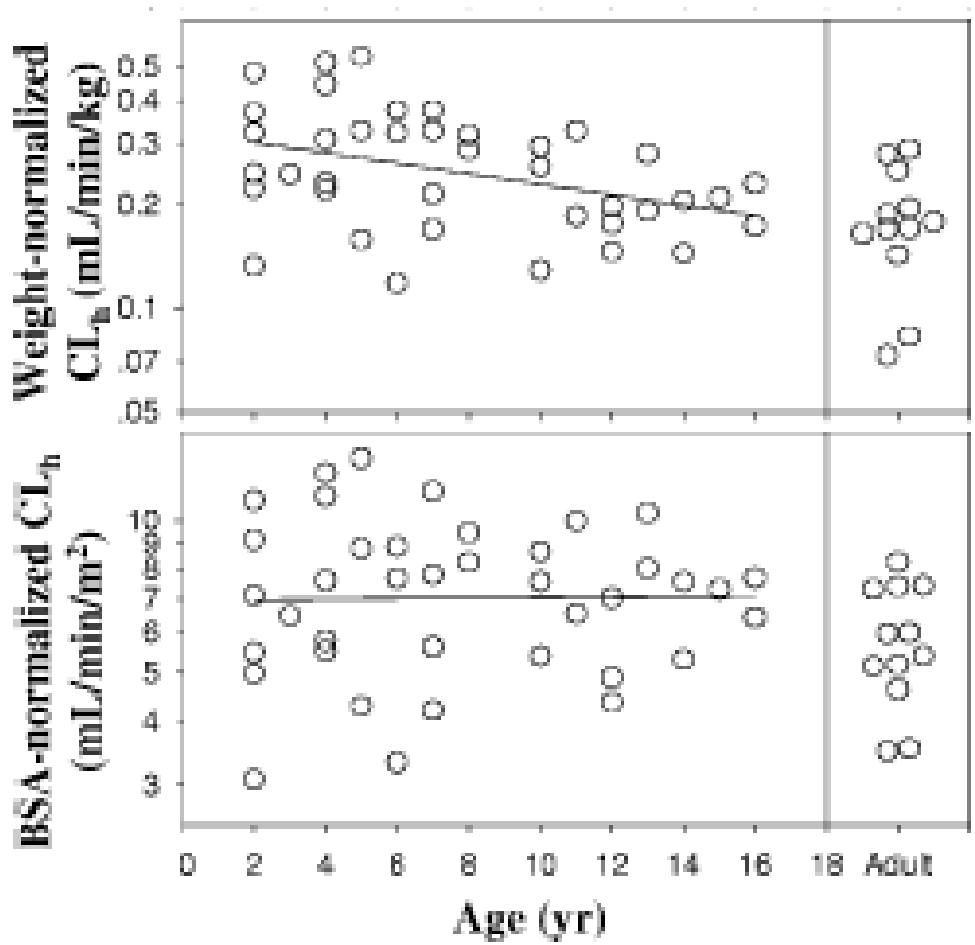


Developmental PK: Fluconazole and Renal Clearance

Age Group	VD [L/kg]	CLt [L/hr/kg]	T1/2 b [hr]
Preterm <1500g, day 1	1.18	0.010	88
day 6	1.84	0.019	67
day 12	2.25	0.031	55
Term neonates	1.43	0.036	28
Infants > 1 to 6 months	1.02	0.037	19
Children, 5 to 15 years	0.84	0.031	18
Adult volunteers	0.65	0.015	30

Saxen 93; Krzeska 93; Lee 92; Brammer 87; Nahata 95

Developmental PK: Caspofungin and Hepatic Clearance

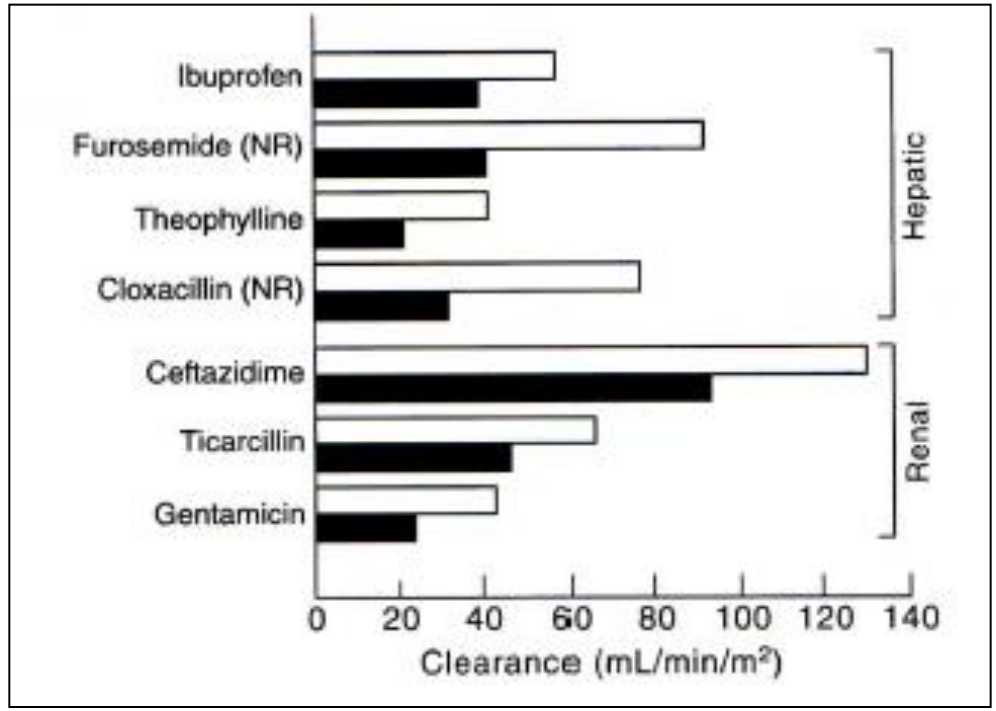


Walsh et al. AAC 2005

Challenges in Pediatric Patients: Effect of Childhood Diseases

- **Effects of pediatric diseases on PK and PD of antimicrobial agents need more study**

- **Enhanced clearance of drugs metabolized by the liver and those excreted by the kidney in patients with CF**



Rey et al. Clin Pharmacokinet 1998

PK Challenges in Pediatric Patients

- **Distribution: larger Vd**
- **Metabolism/elimination: greater Cl**
- **Oral Bioavailability/Absorption:**
  - **may be different**
  - **development of a palatable oral solution may be a major challenge to providing oral delivery**
- ***Additional challenge: Transition to adulthood Rare diseases (i.e., CF)***
- ***Specific challenge: Premature neonates***

PK Challenges in Neonatal Patients

- impact of weight and age at birth / adjusted age
- immaturity of renal and hepatic clearance mechanisms
- protein binding and displacement issues
- penetration of medicinal products into the CNS
- unique neonatal conditions (e.g., ARDS, PDA, etc.)
- unique susceptibilities (e.g., NEC, IVH, ROP, etc.)

➢ ***Highly dynamic setting requiring adaptive dosing with chronic exposure***

Current Concepts of Pediatric Drug Development

Regulatory Guidance for Pediatric Drug Development

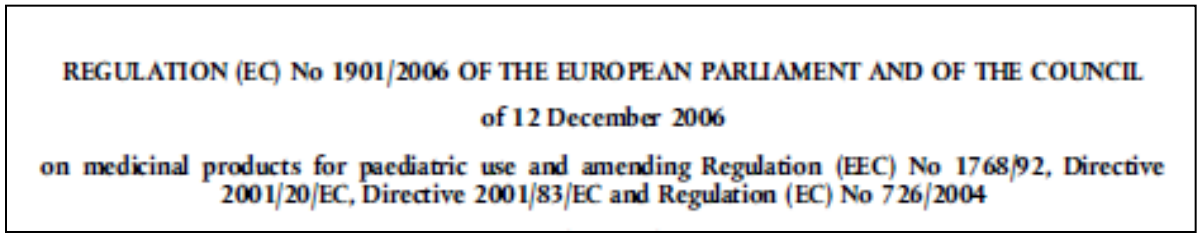
- **clinical studies on pharmacokinetics, safety and tolerance are prerequisite**
- **if underlying conditions, cause of targeted disease and expected response are similar**

➡ **data generated in adults can be used to support documentation of efficacy**

Pediatric investigation usually also requires set of *product quality* and *preclinical toxicology* studies

European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION(CPMP/ICH/2711/99).

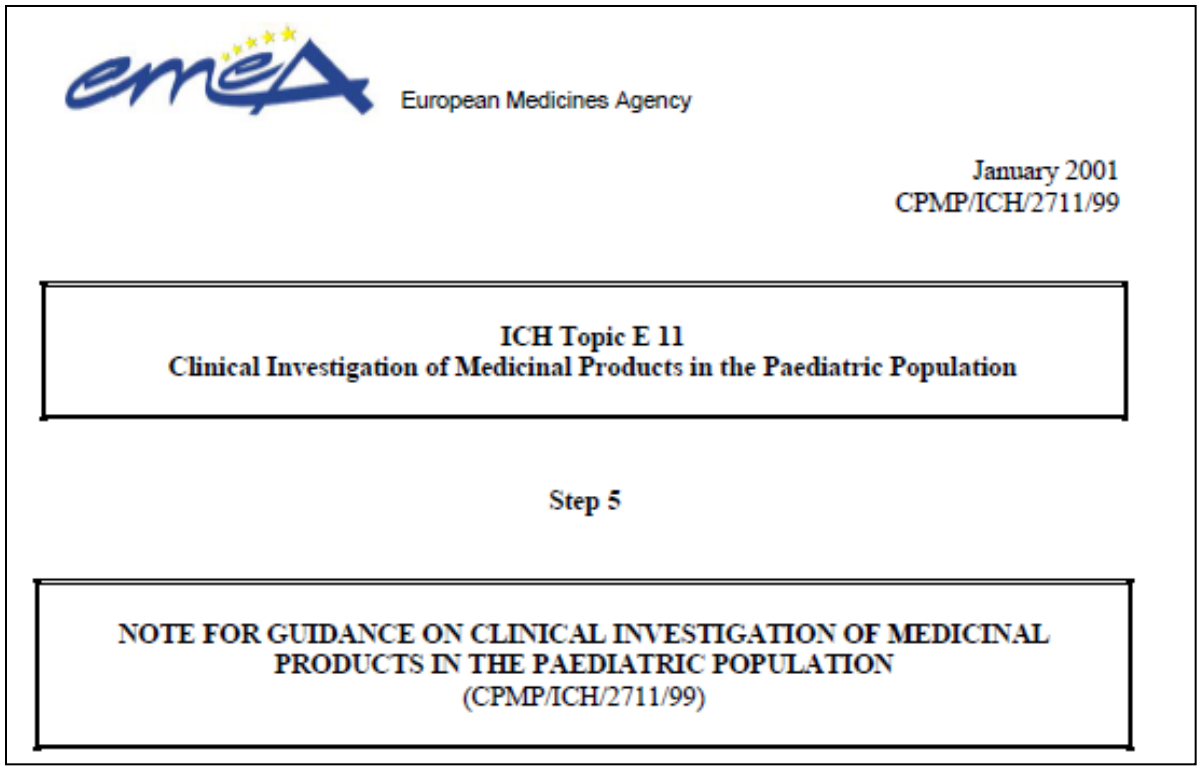
EU Legislation for Pediatric Drug Development ('Pediatric Regulation')



REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004



European Medicines Agency

January 2001
CPMP/ICH/2711/99

ICH Topic E 11
Clinical Investigation of Medicinal Products in the Paediatric Population

Step 5

NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION
(CPMP/ICH/2711/99)

Legislative measures to require pediatric studies

- **for marketed drugs and**
- **new drugs**

that are *likely to be used in a substantial number of pediatric patients*

or *could be an improvement over current treatments* of childhood diseases

➢ ***Goal:***
Increased access to well-studied and safe medicines for children

Regulation (EC) No 1901/2006, as amended

EMA Regulation for Pediatric Drug Development

- Goals:
  - Increase availability of well studied medicines to children
  - To make pediatric information widely available

- **Regulation:**
  - **Requires a *Pediatric Investigation Plan (PIP)***
  - **PIP can be a waiver request, deferral or proposed studies**
  - **Offers 6-month exclusivity when goals are met**
    - **Granted at time of submission of approval for each country in EU**
  - **For drugs approved <2007, *Pediatric Use Marketing Authorization (PUMA)* – 10 years pediatric exclusivity**

Regulation (EC) No 1901/2006, as amended; Raymond et al. Pediatric Drugs 2009;11(1): 9-10

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Regulation for Pediatric Drug Development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. Antibacterial Medicines

Product	Needs
Antibacterial medicines	
Penicillins	
Ampicillin, amoxicillin and cloxacillin	For treatment of various bacterial infections: • Data on PK, dosing, age-appropriate palatable formulation for ampicillin and cloxacillin
Flucloxacillin	For prevention of respiratory infection in cystic fibrosis patients identified by neonatal screening, neuromuscular disorders, non-cystic fibrosis, bronchiectasis, immune deficiency: • Data on PK, efficacy and safety • Data on PK and dosing; age-appropriate palatable formulation for children aged less than 12 years

.....

Nine page list of needed investigations on existing

- ***antibacterial***
- ***antimycotic***
- ***antiparasitic***
- ***antiviral medicines***

in pediatric patients

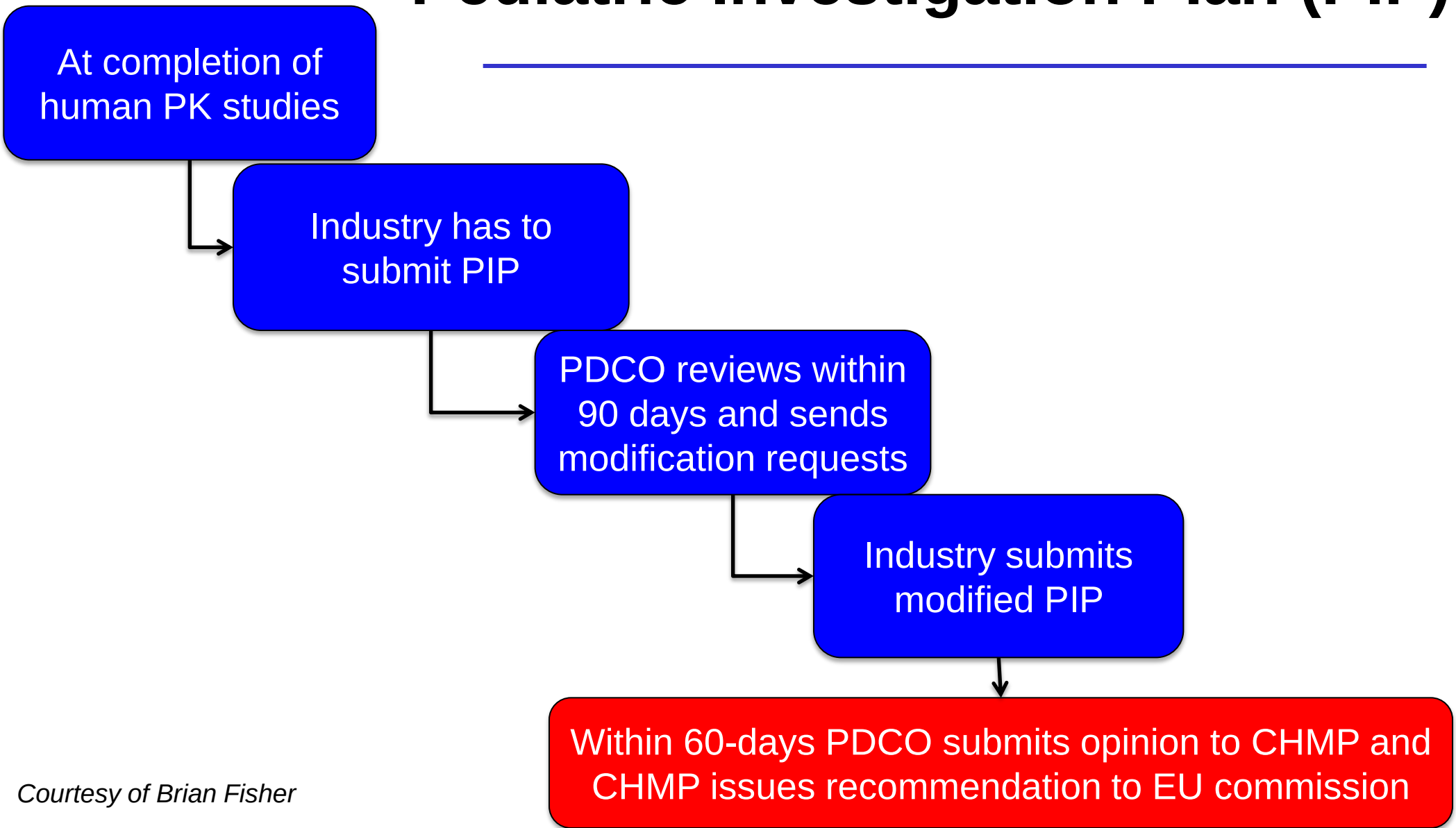
Doc. Ref. EMA/PDCO/287222/2012

What Kind of Pediatric Information is Required from a PIP?

- **Quality related-studies**
  - **Specific to the formulation and mechanism of administration**
- **Non-clinical studies**
  - **Typically studies in juvenile animals**
- **Clinical Studies**
  - **Safety, PK, efficacy/effectiveness studies**
- **Extrapolation/simulation studies**

Regulation (EC) No 1901/2006, as amended; Raymond et al. Pediatric Drugs 2009;11(1): 9-10

EMA: Process for establishing Pediatric Investigation Plan (PIP)



Courtesy of Brian Fisher

Is the legislation working?
EMA and the Pediatric Regulation

- **From its inception in 2006 until June 2013:**
  - **511 pediatric investigational plans reviewed**
    - **65 of these were relevant to infectious diseases**
    - **12% of the PIPs referenced off patent products**
  - **Included only 17/152 agents on the EMA priority lists**
  - **38 PIPs have been completed and passed the PDCO compliance check (this included several new anti-microbial agents) [1]**

** 100 /700 ongoing in Dec. 2015 [2]*

[1] Wimmer et al. Pediatr Drugs (2014) 16:397–406;
[2] 10-year Report to the European Commission – EMA/231225/2015

Is the Regulation the Ultimate Solution?

- **Ample room for improvement**

  - **number of drugs successfully approved is small**
  - **timeliness is an issue for new drugs**
    - **posaconazole - still no pediatric label after > 10 years**
  - **discussions about scientific concepts and efficiency of the PDCO**

- **Also: *Challenges for performing studies not addressed***

Challenges to Pediatric Interventional Trials

- **Children are afforded special protection**
  - **limits research studies that do not provide direct benefit**
  - **only in subjects who have the disease that drug is intended to treat, i.e. no initial normal volunteer testing**
- **Pediatric pharmaceutical studies are challenging**
  - **need experienced pediatric investigators and team at each site**
  - **ID studies: often point of care randomization/informed consent**
  - **concerns from parents/physicians**
- **Pediatric at-risk population is usually small**
- **Competing trials**
- **Drugs are already available**

What could be Improved?

- **Improve infrastructure for pediatric studies**
  - **USA: Pediatric Trials Network (2010)**
  - **EU: European Network for Pediatric Research at the EMA (Enpr-EMA, 2015)**
    - **network of organisations / institutions with expertise to perform pediatric specific studies**
- **Advance legislation to require studies to start sooner**
- **Use of PK/PD concepts and bridging studies**
- **Advance technology to reduce impact on the child**
  - **Reduce blood volume requirements to do PK /toxicity studies**
- **Improve study culture among patients and parents**

10 Year Report to the European Commission – EMA/231225/2015; http://enprema.ema.europa.eu/enprema/showall.php

Conclusions

…what did *Groll* say

- **Pediatric patients are not small adults**
  - **Infections, underlying diseases & comorbidities differ**
  - **PK of antimicrobial agents different across age groups and require comprehensive investigation**
- **Drug approval for children requires study of PK and safety, whereas inference for efficacy of antimicrobial agents is feasible from adult data**
- **Implementation and practice of regulations not perfect but there is hope for improvement**
- **Clinical trials are not easy to conduct and require experience and international collaboration**