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Improving Drug Therapy for Children: The Planned EU Regulation From A Global Perspective

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Agenda

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- Global drug development and regional contributions
- US-triggered pediatric research as starting point
- Planned EU pediatric regulation: challenges & opportunities
- Scenarios for genuine European contributions to pediatric drug research & development
- Outlook

Pediatric Research: Framework established by US Legislation

- Volontary Pediatric Exclusivity: FDAMA* 1997, BPCA** 2002
- Mandatory pediatric development: PREA*** 2003
- Both legislations are linked and sunset 30 September 2007
- Global companies put pediatric assessments *today* into their standard development plans to comply with FDA
- EU pediatric regulation debate does not start de novo
- Ten years of US experience, learning, and research are part of the fundament of the current debate and need reflection

***FDAMA** **FDA** **M**odernization **A**ct ****BPCA** Best Pharmaceuticals for Children Act

*****PREA** **P**ediatric **R**esearch **E**quity **A**ct

EU Doesn‘t Start from Zero: Research Stimulated By FDAMA & BPCA

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- Potential research targets: clinically relevant off-label use
- Deliverable: ***research performed***.
- No need for a positive result – also an identified counterindication has high clinical value
- Most patent protected drugs have today US PE data on
  - PK/PD and dosing in younger populations
  - Pediatric formulations
  - Counterindications in children
  - New indications
- Granted written requests (**WR**s) and pediatric exclusivities (**PE**s) cover a wide range
  - Same indications as in adults investigated in children
  - Completely different indications investigated in children

Granted US PEs: Examples

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- Orlistat (Xenical): Obesity of adolescents
- Oseltamivir (Tamiflu): Influenza in children 1-12 years old
- Atorvastatin (Lipitor): new indication heterozygous familial hypercholesterolemia
- Tamoxifen: safety & efficacy in McCune-Albright Syndrom
- Alendronate: safety & efficacy in osteogenesis imperfecta (OI)
- Vinolrebine: Negative result (“no meaningful clinical activity“) of investigation of safety & efficacy in various solid tumors
- Detailed statistics: www.fda.gov

Which Research Is Stimulated By PREA?

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- PREA refers only to same indication in children as in adults
- Covers chemical products as well as biologics
- Orphan drugs are exempted
- FDA did for several medicines invoke PREA once companies had refused to agree upon an issued WRs
- No statistics yet available on www.fda.gov
- Has in general led to inclusion of pediatric aspects into the general drug development process

Inclusion of Pediatric Aspects into the General Drug Development Process

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Adults	Children
Basic research → NCE* / NBE**	Animal models? Age specific receptors?
Identification of potential diseases	Mechanism of disease? Epidemiology? Serum concentration ↔ efficacy?
Decision to go into man	Accelerated development in child?
Preclinical testing	Shift tox studies to earlier phases. Decide about juvenile animals
Technical R&D	Pediatric formulation(s) / delivery systems
Phase I: Safety & PK/PD data	Extrapolation models / first ped studies
Phase II-III: identify suitable centers	Identify suitable centers. Prepare specific informed consent & assent
Phase IV	Safety monitoring

***NCE** New Chemical Entity ****NBE** New Biological Entity

Global Consequences of Pediatric Legislations

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- Common feature PREA / EU: companies have to *think* of children early – together with Health Authorities!
- Companies have to increase their pediatric competency
  - Build up pediatric department, or ...
  - Establish cross-functional expert group, or ...
  - Buy external competence @ appropriate consultant or ...
- Health Authorities will increase competency & demands
- New technologies will be increasingly used, e.g. trial simulation, extrapolation elder → younger children, new statistical methods
- Will increase the costs of drug development
- Will make more pediatric pharmeceutical knowledge available

EU-Triggered Research: Categories

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- Medicines in early development, submission after 2010
- Medicines in clinical development, submission before 2010
- Marketed medicines, patent protected until ~2012
- Marketed medicines, patent protected until ~2009
- Marketed medicines, patent expiry soon
- Off-patent medicines

Medicines in Early Development, Submission after 2010

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- Pediatric assessments have already been discussed with FDA or will be done @ EOP2 (end of phase 2) meeting
- Companies have preliminary ideas about development in children, but there is time to modify for additional PC requests
- Pediatric Scientific Advice free of charge will be used
- Companies will have sufficient time to adapt development plans to both FDA and EMEA PC

Medicines in Clinical Development, Submission between 2007 and 2010

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- Pediatric discussions with FDA are in process
- EMEA PC will start to give input once it is fully functional and has worked off backlog of very urgent projects
- EMEA PC will ask for modifications or additional requests beyond FDA-negotiated / FDA-triggered requests
- Pediatric Scientific Advice free of charge will be used
- Input will be additional to first FDA-triggered development plans

Marketed Medicines, Patent until ~2012

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- Due to US-triggered research, most have data available on PK/PD & dosing in children, pediatric formulations, counter-indications in children, additional indications
- PIP should address **additional** clinically meaningful research targets: further indications & age groups, longer observation period, rare diseases
- Companies will proactively seek these targets for reward
- Will require an ***interpretation*** of the regulation
- With sufficient time left until end of patent, agreement on reasonable PIPs between PC and companies appears probable
- There will be sufficient time to perform the planned trials

Marketed Medicines, Patent until ~2009

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- Due to US-triggered research, most have pediatric data
- PIP should address **additional** clinically meaningful research
- Companies will proactively seek these targets for reward
- Will require an ***interpretation*** of the regulation
- Companies can ask for Scientific Advice today - with fees - and free of charge once the regulation is in force
- With patent expiry coming soon, EMEA PC will need to evaluate & approve PIPs fast during first months of its existence
- Time for execution of agreed upon development plans will be limited

Marketed Medicines without SPC

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- For several products there is no SPC with potential prolongation beyond patent expiry or data exclusivity
- Additional pediatric research will for these products require additional investments
- These will not be balanced by additional income at end of patent life

Marketed Medicines, Patent Expiry Soon

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- EU regulation comes too late for a PIP with potential SPC extension
- Copies are being prepared by generic companies
- PUMA (Pediatric Use Marketing Authorisation) 10 years data exclusivity might justify research to defend part of brand *if* calculable:
  - **When** request PUMA licence: first day of EMEA PC?
  - **How** request PUMA: PUMA PIP? Declare research intention?
  - PUMA products will need higher price than generics
  - Condition: no substitution of PUMA products by generics
- EU regulation might evolve into a working framework.
- EU draft regulation: probable not sufficient for company calculations
- Further condition: EU-wide national buy-in: prevention of generic substitution is in the remit of *national* governments & agencies

Marketed Medicines, Patent Expired: PUMA

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- Generic copies are already on the market
- Originating company has stopped investments & research
- Generic companies that consider PUMA will calculate the potential return of their investment. They will ask:
  - Who gets PUMA?: company that declares intention to do research? / that starts first trial? / that submits first data?
  - Can PUMA be discussed with EMEA PC before patent expiry?
  - Higher price for PUMA products than for generic copy?
  - Prevention of substitution of PUMA products?
- PUMA might offer niche opportunities for small/medium companies
- For calculation implementation rules will be required
- Further condition: EU-wide national government / agencies buy-in

Marketed Medicines, Patent Expired: MICE

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- MICE (Medicines for the Children of Europe) program was anounced March 2004
- Should offer tenders & grants for research in drugs without economic incentives
- The name ‘MICE‘ will not be used
- A grant program is still planned
- Assigned budget will depend on EU Commission‘s priorities

Questions

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- Is the EMEA SAWG prepared for the tsunami of pediatric Qs?
- Will the EMEA PC over the first months of its existence prioritize PIPs on medicines with nearing patent expiry?
- Which additional research requests beyond FDA-triggered data will the EMEA PC put into the PIP?
- How far will the EMEA PC be committed to reward research in rare diseases?
- How will PIPs look like for drugs without SPC?
- How can the EU Commission be convinced to provide considerable funds for MICE?

More Questions

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- Will the national authorities prevent substitution of PUMA products by generics through different listing?
- How will PUMA projects be handled operationally?
  - First intention to perform pediatric research declared?
  - First pediatric trial initiated?
  - First submission of pediatric data?
- Can a generic company request a later PUMA in the period before patent expiry?

Operational Conclusions

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- The handling of the EU regulation still needs to be molded
- Patented drugs: potential incentives disappear @ patent expiry
  - The farer away patent expiry, the more EMEA PC will have time to give strategic input into pediatric development
  - The nearer patent expiry the more time pressure
  - During transition the EMEA Scientific Advice Working Group (SAWG) might serve as communication channel
- Off-patent drugs: PUMA incentive must be calculable. Will need implementation rules and support on national level
- MICE program will be crucial for older off-patent medicines. Apart from a new name it will need a significant budget

Conclusions

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- The EU draft pediatric regulation shows the will of EU Commission & EMEA to facilitate pediatric research in Europe
- It adds momentum and helps to remove mental barriers
- To transform the vision of a stronger place of Europe in pediatric research into reality, an intensified dialogue between the partners in health care – regulators, health authorities, patients & parents, pharmaceutical industry - will be crucial

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Thank You!

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Back-Ups

Abbreviations

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BPCA Best Pharmaceuticals for Children Act

MAA Marketing Authorisation Application

PREA Pediatric Research Equity Act

PE Pediatric Exclusivity

HA Health Authority

PC Pediatric Committee

SAWG Scientific Advice Working Group

MICE Medicines Investigation for the Children of Europe

PUMA Pediatric Use Marketing Authorisation

When Should Drug Development Start In Children? - ICH E 11 Scenarios -

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1. **Medicinal products for diseases predominantly or exclusively affecting children**
   - ➔ *Development in children only, e.g. lung surfactant*
2. **Medicinal products intended to treat serious or life-threatening diseases, occurring in both adults and children, and currently no or limited therapeutic options available**
   - ➔ *Pediatric development should begin early after initial safety data and reasonable evidence of benefit*
3. **Medicinal products for other diseases and conditions**
   - ➔ *Less urgent in children, start development in phase IIIb/IV*

Consequences of Early Start of Pediatric Envolvement

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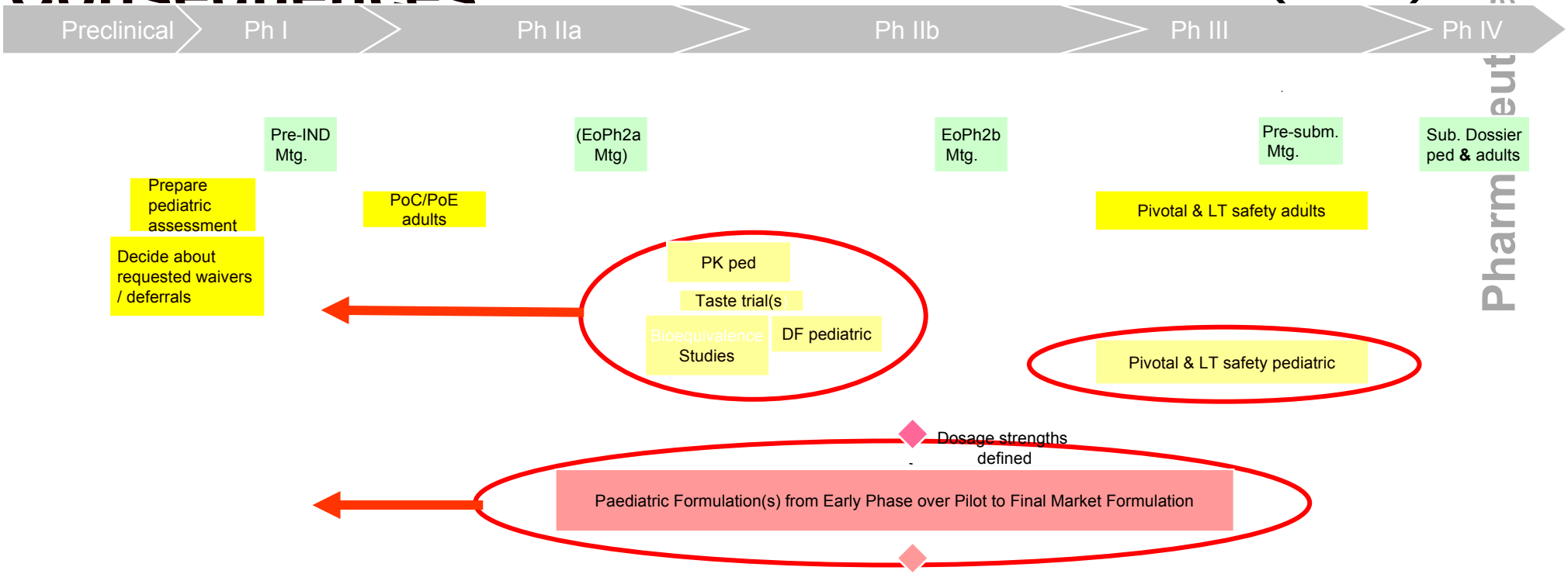
- To the child: risk of exposure to a new substance
- The company: allocation of additional resources
- Shifts many development steps into an earlier stage
- All these investments are lost if the project is abandoned

⟶ Needs to be carefully considered case by case based on

- ➢ Mechanism of disease in children
- ➢ Risk / benefit assessment
- ➢ Frequency of the disease in children
- ➢ If applicable, specifically for the different age groups

Accelerated Pediatric Development: Consequences



Analytical method development
Blood dist./proteinbg. across species
in vitro metabolism across species
Radiolabeled synthesis
Rat ADME, QWBAR i.v.
p.o. rising dose/rat & dog
Safety pharmacology
Ames test (5 strains)
in vitro mutation in mammalian cells
p.o. 2-4w tox study in rats (incl.TK)
p.o. 2-4w tox study in dogs (incl. K)
i.v. acute tox study in rats & mice

Route feasibility feed
mouse, rat (car)
13w DRF mouse, rat (car)
Safety pharmacology suppl.
26w tox study p.o., rat, dog
Embryofetal dev po DRF rabbit
Embryofetal Dev po rabbit, rat

Fert. early. embr. dev, po, rat
Pre-/Post natal p.o., rat
Milk excretion study

Carcinogenicity p.o. mouse, rat
Local tolerability i.v. rabbit
Mechanistic toxicity
2w i.v. toxicity rat, dog
Ames & V79CA impurities
39w tox p.o. dog, monkey

EU Draft Pharmacovigilance (PV) Guidance

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- “Guideline on Conduct of Pharmacovigilance for Medicines used by the Paediatric Population“
- http://www.emea.eu.int/pdfs/human/phvwp/23591005en.pdf
- Published for consultation summer 2005, consultation period expired 31 January 2006

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