Life Science Forum Basel

Challenges and New Opportunities around Product Development in the Life Sciences

June 6th 2013, 12:00 h

Biozentrum/Pharmazentrum, Universität Basel, Klingelbergstrasse 50, 4056 Basel

Why Are Children So Difficult?

US & EU Pediatric Legislation And Its Impact On Drug Development

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Labels A Century Ago

Source: www.wellcomecollection.org

Modern Drugs: Therapeutic Potential & Danger

- 1937 a liquid anibiotic was introduced
- Solvent: Ethylen Glycole; highly toxic; no tox testing. > 100 deaths, $^1/_3$ children
- Led to revision of FDA legislation
  - Next catastrophe: Thalidomide1962
  - Ten US cases through ‘clinical studies’
  - Led to the Kefauver-Harris amendments

Modern Drug Labels: Started With US Legislation

- Date back to US legislation 1962: enforced proof of efficacy. Use in children mostly off-label since then.
- Voluntary Pediatric Exclusivity (PE): BPCA* 2007 after first laws 1997 & 2002. Biologics excluded.

- Mandatory ped development: PREA*** 2003. All age groups. Biologics included. Applies to same indication as in adults only.

- Re-authorized 2012 as FDASIA***
- BPCA &PREA have resulted in multiple pediatric research on patented drugs. Both seen by FDA as major success

*BPCA Best Pharmaceuticals for Children Act

**PREA Pediatric Research Equity Act

***FDASIA FDA Safety & Innovation Act

EU Pediatric Regulation

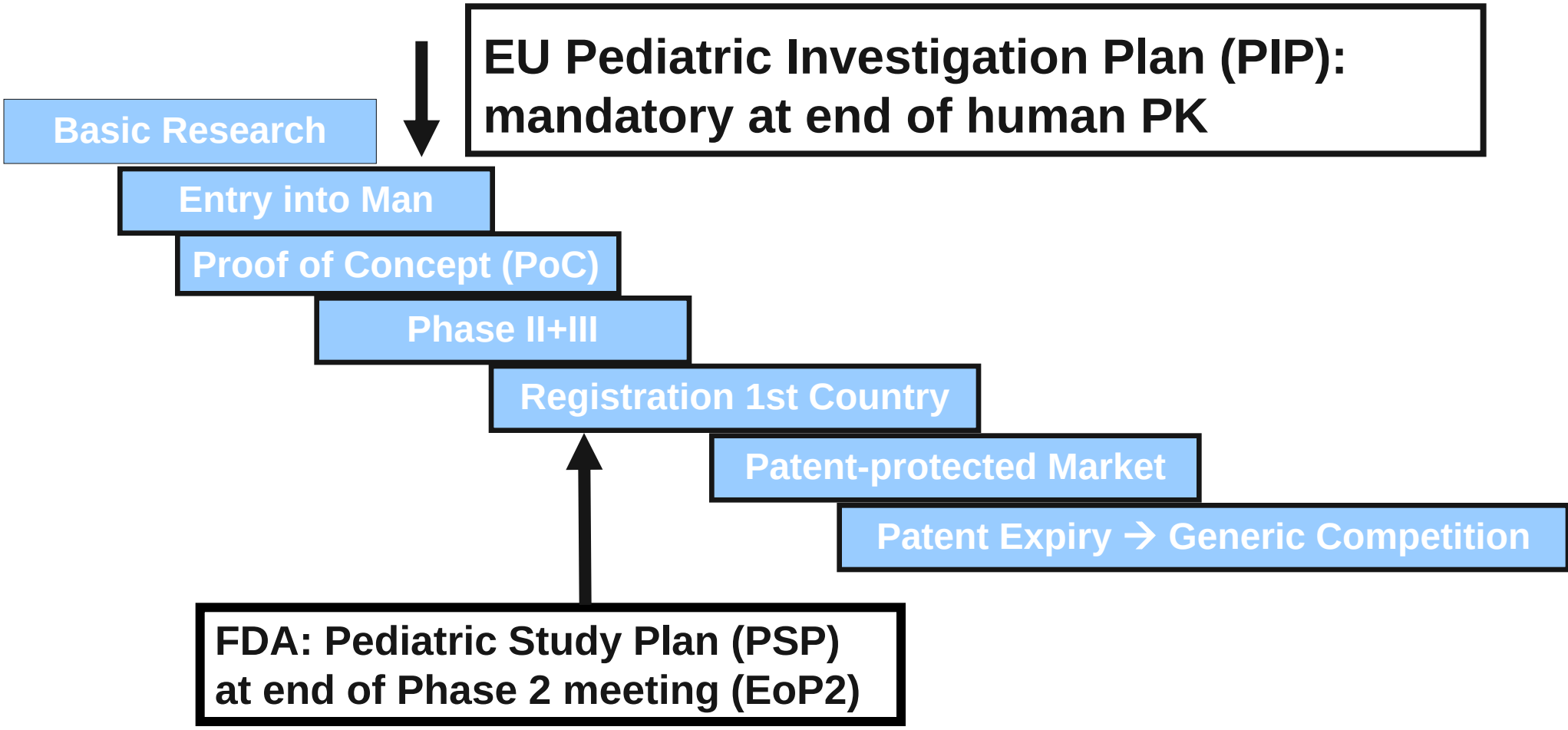
- In force since January 2007
- Combines mandatory development  with reward 
- Pediatric Investigation Plan (PIP) mandatory end of human PK
- PIP must cover all age groups
- Pediatric Committee (PDCO) assesses PIPs, waivers & deferrals
- Reward of six months SPC* prolongation

*SPC Supplementary Protection Certificate

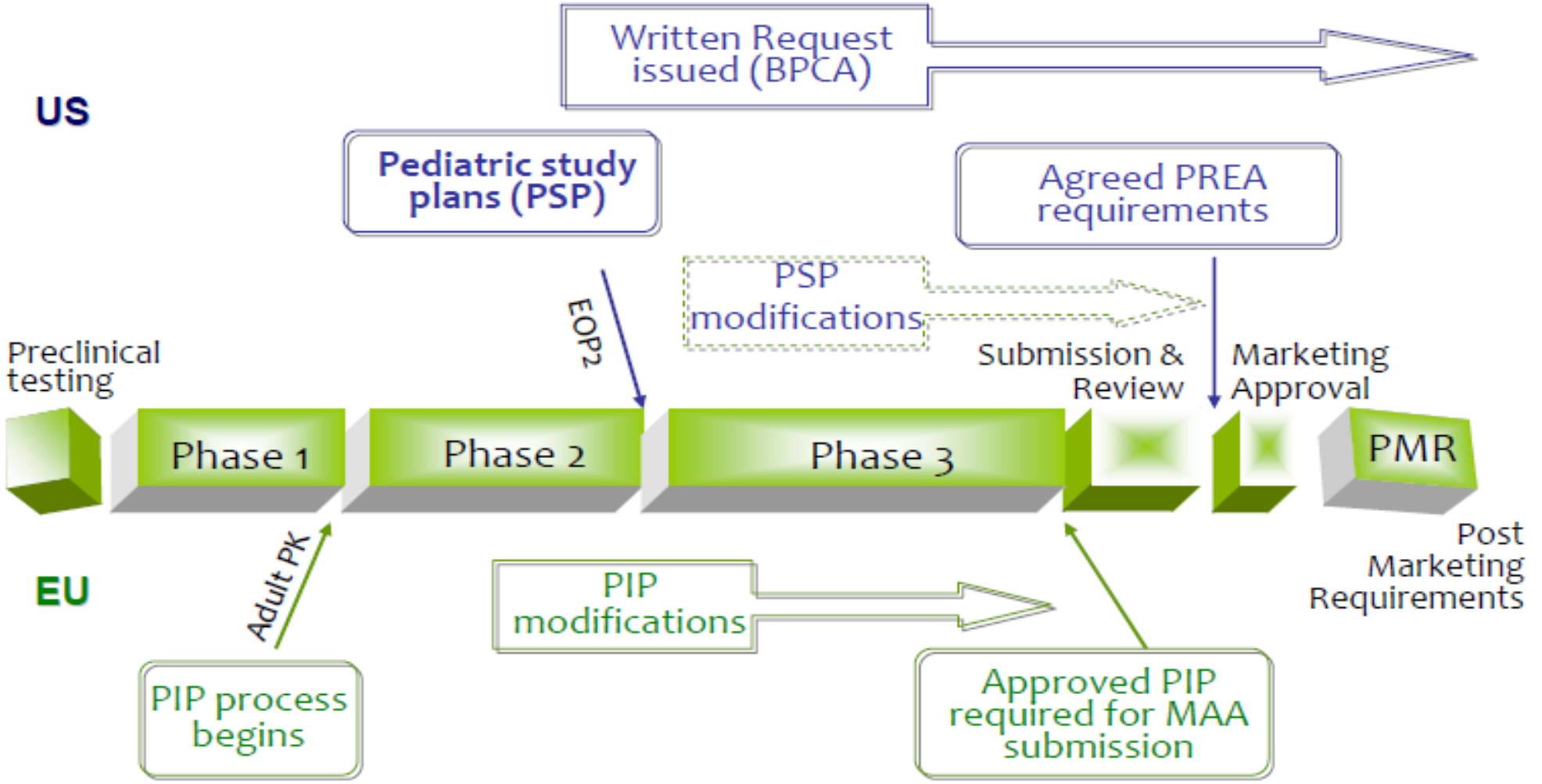
EU Pediatric Regulation: Core Elements

- FDA started with looking for ‘some‘ pediatric data
- EMA wants, as far as possible, full pediatric indication(s)
- Want the necessary data as soon as possible for marketed drugs and as early as possible for new drugs
- Expect each company to be knowledgeable + up to date
- EMEA / PDCO style has evolved since 2007. Claim to be science-driven, but have developed a tough attitude. So far backed by the EU Court of Justice

Regulatory & Scientific Challenge: Earlier Inclusion of Children In Drug Developemnt

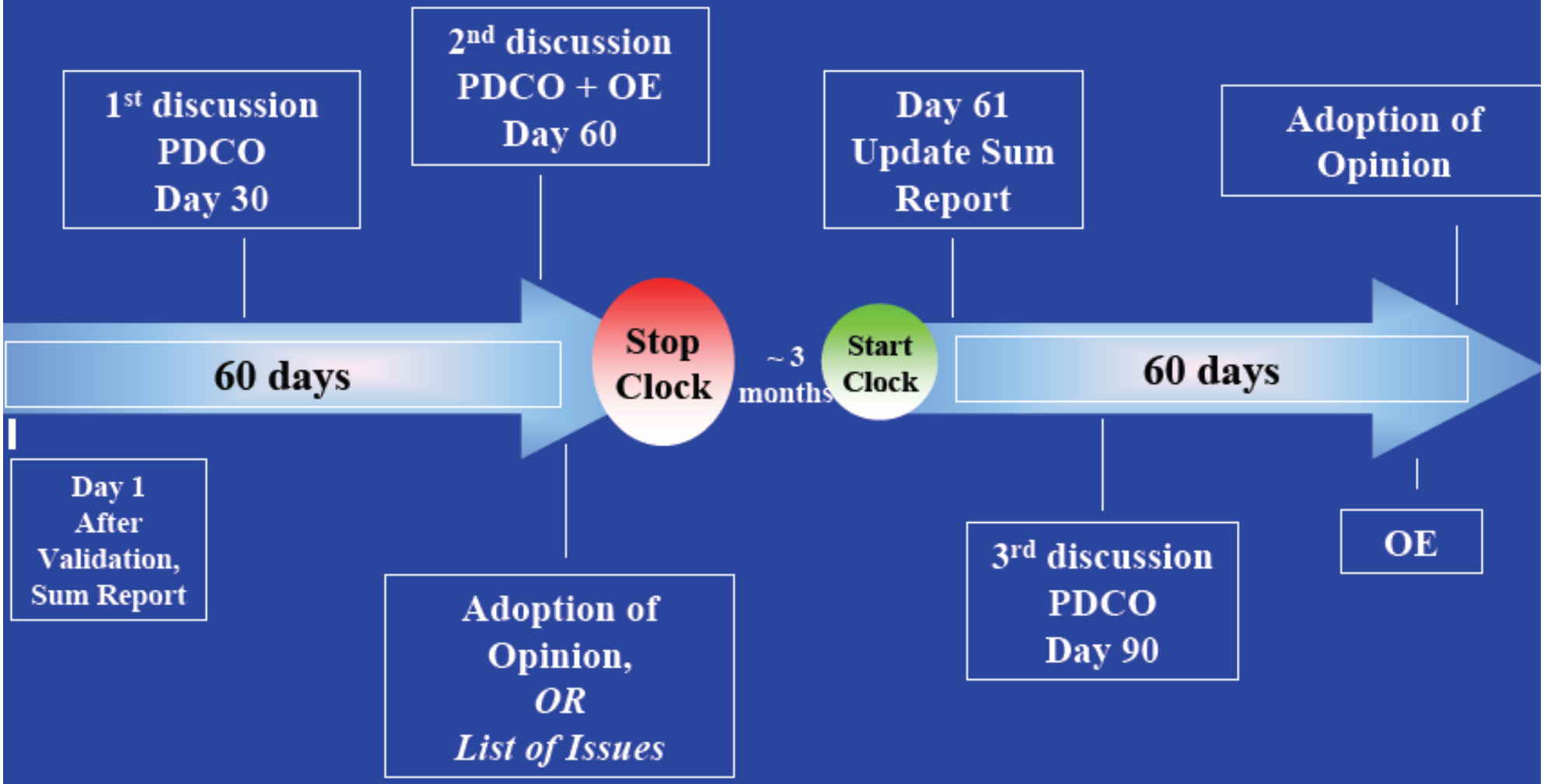


Pediatric Planning in the Drug Development Process



Marketing Application Authorization [MAA]

Overview PIP procedure



OE= oral explanation

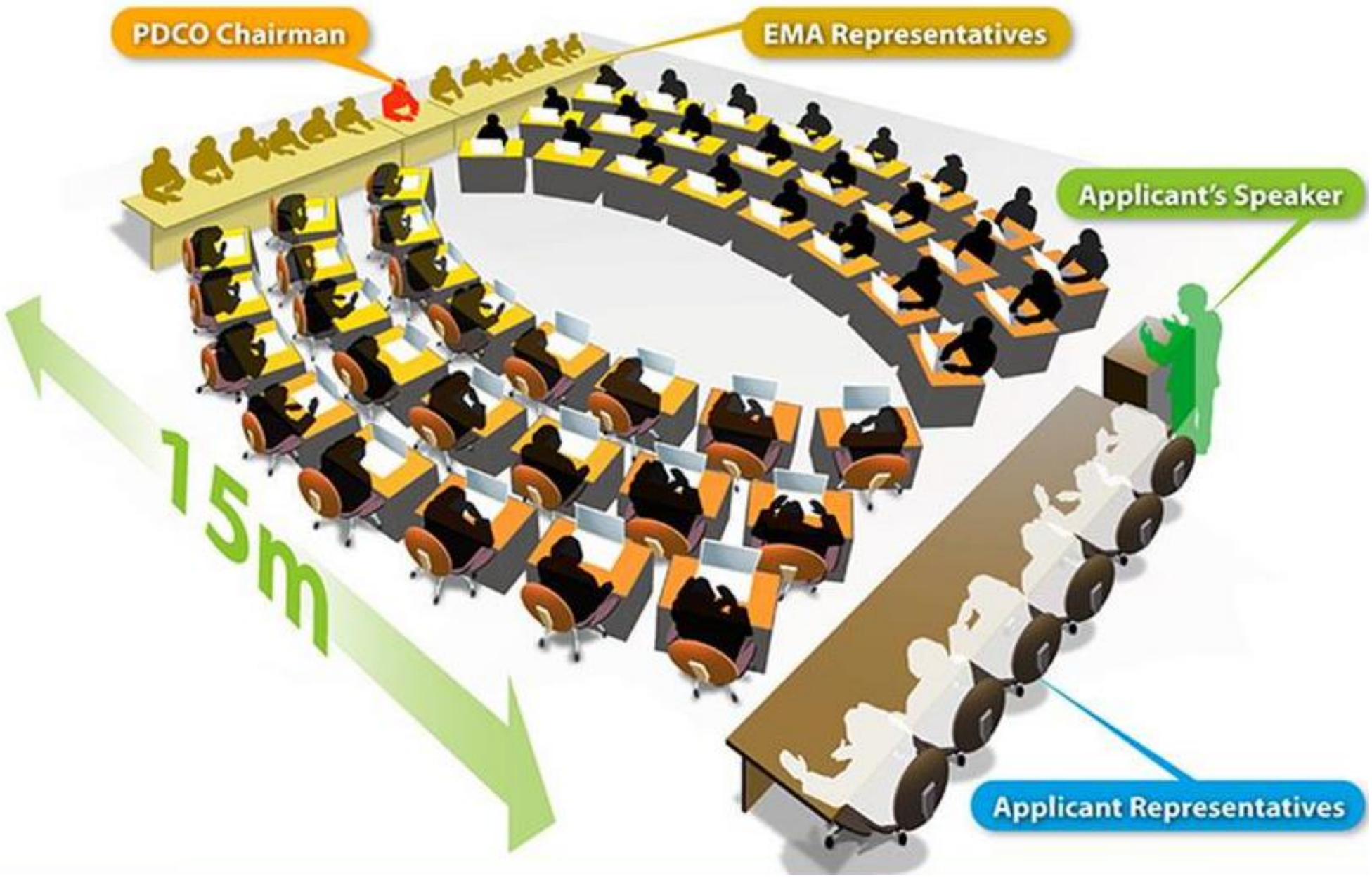
PIP Core Elements

- Overview over new drug, targeted disease in adults & children 0-18 y
- Non-Clinical: juvenile animals etc
- Quality: technical development, e.g. tablet, minitablet, pellets, liquid
- Clinical: Modelling & Simulation, Safety & Efficy trials, extrapolation

PIP Procedure: Milestones

- 3 months before start of procedure: send Letter of Intent (LoI)
- 1 month before start of procedure: submission. Validation by EMA, Qs to be answered fast. Procedure starts after validation
- Day 30 discussion + report (D+R): no action required from applicant
- Day D+R: lists requested modifications: must be answered
- Day D+R: lists requested last modifications
- Day 120: Only chance for F2F Oral Explanation (OE)

PDCO Oral Explanation: Room & Sitting



Case Study Coronary Artery Disease (CAD)

- Nykomed requested a full waiver for Acusphere, an ultrasound diagnostic contrast microbubble to identify coronary artery disease (CAD). Disease listed on class waiver list
- EMA-defined condition: “Visualisation of myocardial perfusion (MP) for diagnostic purposes”. Children can have MP deficits
- Negative opinion 2008
- Applicant took EMA to EU Court of Justice; 1st instance backed EMA
- US originator company negotiated a new PIP with EMA, agreed 2011
- Nykomed continued. EU CoJ backed EMA DEC2011: otherwise, companies could easily circumvent obligation to pediatric development
- The two EU CoJ decisions have very much strengthened EMA

PIP Decisions

- So far > 1000 PIPs have been submitted
- The key elements are published, but not the details
- Details are always confidential
- Nevertheless, we can see trends in specific areas
  - Pediatric oncology
  - Joint injuries
  - Vaccines
  - Drugs for preterm newborns
  - Drugs developed only for children
  - Rare diseases

Case Study Rare Disease (presented at EFGCP/DIA/EMA Pediatric Conference 2012)

- NBE developed only for use in premature neonates → rare condition
- Scientific Advice with German BfArM and Swedish MPA 2008, with CHMP in June 2009 to discuss clinical development plan
- PIP submitted FEB2010, OE JAN2011
- Agreement with PDCO on a plan that contained only minor modifications compared to the clinical program agreed with CHMP 19 months earlier
- Clinical program delayed at least 9 months

Ivacaftor (Kalydeco) for CF (Cystic Fibrosis)

- CF, a genetic disorder, affects epithelial cells in the entire body resulting in respiratory, endocrine, GI & reproductive abnormalities
- Caused by defect(s) in the CF transmembrane conductance regulator (CFTCR) protein. Sweat, digestive fluids, and mucus are too thick.
- Life expectancy 1950: 2 (two) years; 2012: ~ 40 (forty) years
- Until 2012 treatment with mucoactive agents (e.g. DNAse), antibiotics, inhaled beta agonists, and other anti-inflammatory drugs
- ~ 5% of CF patients have the G551D mutation
- Kalydeco approved by FDA JAN2012 for patients $\geq$ 6 y with the G551D mutation; registration based on two 48-week, placebo-controlled studies with 213 patients, one in $\geq$ 12 years & another in 6 - 11 y; good S&E; lung function improvement.

Ivacaftor (Kalydeco)

- PIP submitted 2008, first RfM (request for modification) 2009, 7th modification accepted DEC2012 (EMEA-000335-PIP01-08-M07)
- PIP studies in the DEC2012 version: 1 quality, 1 non-clinical, 9 clinical studies to be performed until December 2016. Of the clinical studies, 2 in adolescents, 4 in > 6 y, 1 in 2-5y, 1 in < 2y, one in CF patients ≥ 6 y with non-G551D CFTR gating mutation
- This drug is already approved in children ≥ 6 years!
- What is that PIP good for? Was the PDCO helpful in developing this breakthrough medication? Or was it an obstacle?
- Well …. No EMA registration without a PIP. Even if the company develops a life saving drug in a pediatric disease
- EMA keeps only the most updated version of the modified PIP on its website. Details are confidential between Vertex and EMA.

Lumacaftor for CF

- Developed for CF patients with the F508del mutation in CFTR
- This mutation is found in ~ 60% of CF patients
- PIP submitted in 2011, accepted JUL2012 EMEA-001173-PIP01-11
- 15 PIP measures
  - 2 quality studies
  - 7 juvenile animal studies
  - 6 clinical studies
- Vertex develops this drug in a pediatric disease!

Melanoma

- Class waiver for melanoma was revoked
- Justification: 1.7/ 100’000 15-19ys olds in US statistics Surveillance, Epidemiology & End Results (SEER), www.seer.cancer.gov
- 6 PIPs if you search with ‘melanoma’: Ipilimumab (2); MAGE-A3 recombinant protein; GSK1120212; GSK2118436; RO5185426
- Deducing $^{2}I_{5}$ from 1.7 (18/ 19 y old are adults) leaves maybe 1 in 100’000 which may be PDCO limit for ultra rare disease? Not official
- And: adolescent melanoma often not yet metastasized. In contrast to adults not all patients need systemic treatment
- Separate clin studies in adolescent melanoma ethically questionable
- Adolescents ***should have the right*** to participate at adult studies, but with these ase numbers no statistically significant results possible

EU Ombudsman

- EU Ombudsman is an institution derived from Nordic Justice, aiming at ensuring fairness in public administration
- Two companies complained against EMA/PDCO @ EU ombudsman: Candesartan had been given a PIP, two other sartans a waiver.
- Ombudsman decided the complaint fell under ‘maladministration’
- Enquiry showed that the EMA-given reasons for selecting candesartan were not reflected in the reasoning for the waivers for the other sartans
- The enquiry resulted in recommending, inter alia, EMA guidelines to assist PDCO to follow a coherent structure of analysis in future cases
- Ombudsman cannot overrule decisions, but can embarrass an agency.
- EU Ombudsman’s office will be happy to receive more complaints
- Website: www.ombudsman.europa.eu. Draft recommendations:

www.ombudsman.europa.eu/en/cases/draftrecommendation.faces/en/11553/html.bookmark

Interim Reflections

- Is consideration of children possible at all in drug development?
- Some areas: yes. E.g. use of antibiotics in babies
- Some areas: no. E.g. terbinafine for fungal skin affections. Pivotal trials for FDA registration: > 2000 patients; 2 < 18 years. Statistical power?
- Where disease is very rare, case numbers too low for statistical power
- Areas where the PDCO is probably doing more damage than good: orphan diseases, pediatric diseases, vaccines
- Ethics committees now confronted with two opposite challenges
  - Clinical trials in children are ethical and necessary, ***and***
  - Some PDCO-triggered studies should be refused

Societal Impact of EU Pediatric Legislation

- Very high ambitions, partially based on wishful thinking
- Increases costs of drug dev; for big pharma costs still marginal.
- Can be different for an individual small / medium company
- SME office @ EMA offers help, but PDCO treat all applicants equally
- Takes decision power away from originating companies
- Does not contribute to pharmaceutical innovation in Europe
- Has increased the weight of academic pediatrics
- Most clinicians have still positive general view, but criticism starts
- Assessment of relation of resources assigned to resulting clinical benefit for children almost impossible due to confidentiality

Conclusions

- Drug development no longer possible without considering children
- EU pediatric legislation & administration: Mosaic of goodwill, scientific input, reasonable decisions, abuse of power; lack of checks & balances, disproportionate use of resources, limited clinical benefit
- PIP skills needed: know PDCO, its decisions; good negotiation skills;
- Potential for saving resources is highest during early PIP preparation
- Aim for individual company: negotiate PIP that will serve child health in the far future and lets company survive
- Legislation will not disappear
- I hope you enjoyed this talk ……there will be many more conferences

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Next Pediatric Conferences

- 8th July 2013 SMI Ped Drug Development Masterclass London, UK
- 24/25 September 2013 DIA/ EFGCP/ EMA Pediatric Conference London, UK
- 31st March – 02 April 2014 SMI Pediatric Conference London, UK
- 31st September/ 1st October 2014 EFGCP/ DIA/ EMA Pediatric Conference London, UK

Thank You For Your Attention!

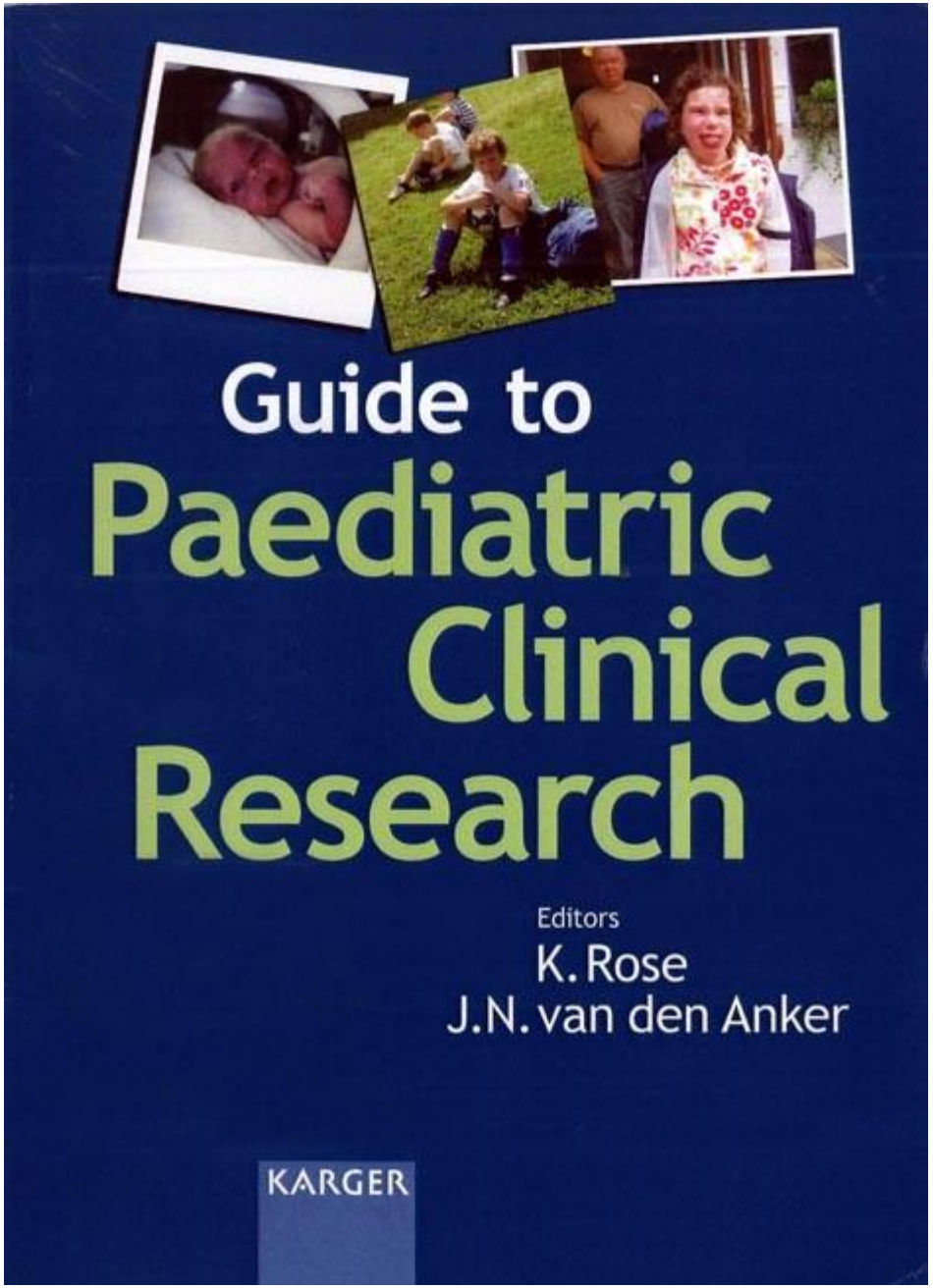
Back-Ups

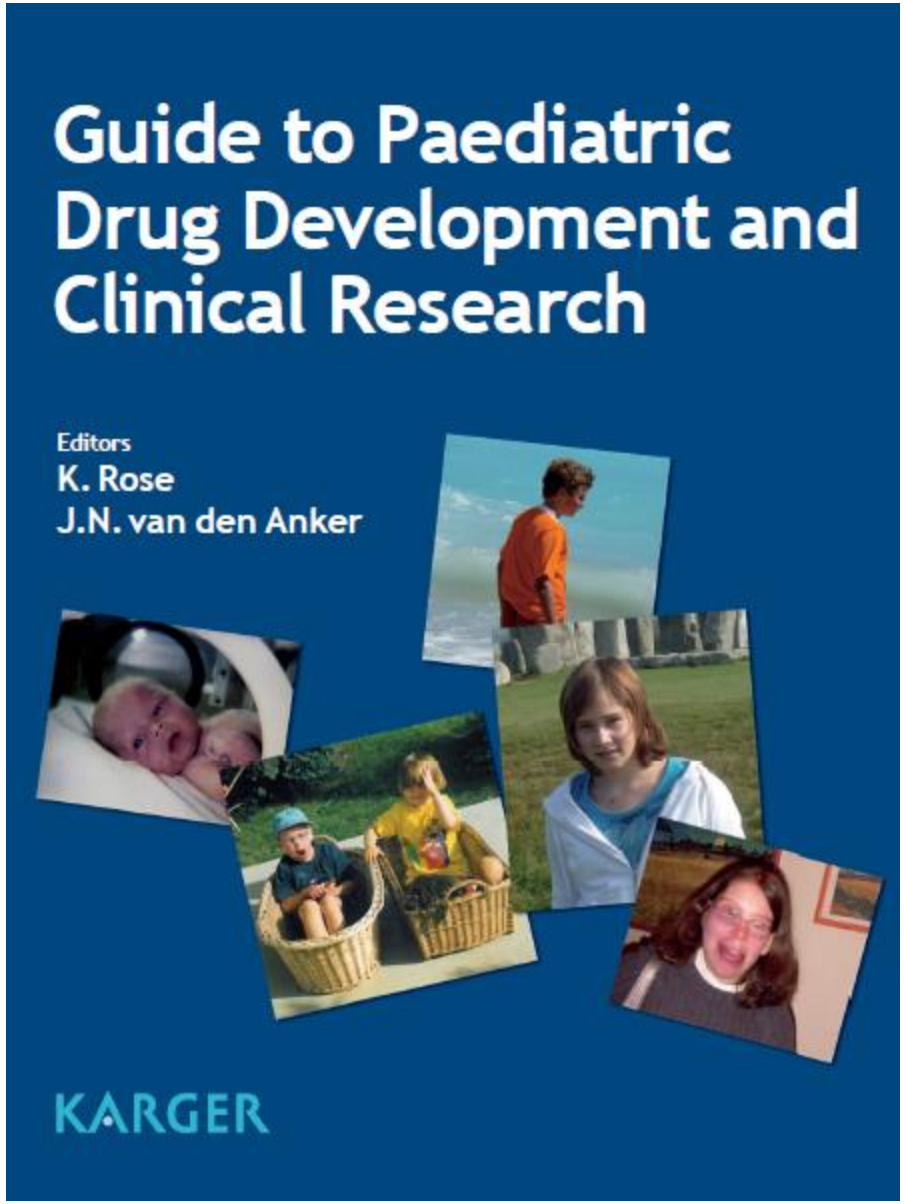
EMA Decisions Perflubutane

- EMA decision of 28 November 2008 on the application for product specific waiver for perflubutane EMEA-000194-PIP01-08 in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended. http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005753.pdf
- EMA decision of 18 May 2011 on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for perflubutane (EMEA-000194-PIP03-10) http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500107411.pdf

EU Court of Justice Decisions

- Order of the President of the Court of First Instance of 24 April 2009 – Nycomed Danmark v EMEA (Case T-52/09 R). http://curia.europa.eu/juris/document/document.jsf?text=&docid=73453&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=327397
- Judgment Of The General Court (Third Chamber) 14 December 2011. http://curia.europa.eu/juris/document/document.jsf?text=&docid=116583&pageIndex=0&doclang=EN&mode=doc&dir=&occ=first&part=1&cid=234507





Guide to Paediatric Drug Development and Clinical Research
Editors: K. Rose, Munich; J.N. van den Anker, Washington D.C./Rotterdam
■ + ■ p., 17 fig., 23 tab., hard cover, 2010
ISBN 978-3-8055-9362-5

Lumacaftor for CF: PIP Measures I

Quality

1. Development (Dev) of a film-coated tablet.
2. Age appropriate oral formulation for children < 6 y; testing of acceptability, palatability, & compatibility with common food & drinks.

Non-Clinical

3. 6-month oral (gavage) tox & toxKin with lumacaftor and VRT-0995096 in rats with a 1-month recovery
4. 3-month oral gavage toxicity and toxicokinetics study with lumacaftor, ivacaftor, and VRT-0995096 in rats with a 1-month recovery
5. 12 month oral (gavage) toxicity and toxicokinetics study with lumacaftor in Beagle dogs with a 1-month recovery
6. Developmental and Perinatal/Postnatal Repro Tox study in rats, including postnatal behavioral/functional evaluation
7. Fertility & early embryonic dev in rats with lumacaftor and VRT-0995096
8. Oral dose range finding study in juvenile rats (VX-809-TX).
9. Oral tox & toxKin in juvenile rats with 4-week recovery

Lumacaftor for CF: PIP Measures II

Clinical

10. OL PG MC to evaluate PK of lumacaftor, ivacaftor & major circulating metabolites in CF patients with F508del-CFTR mutation 6 - <18 y
11. R DB PC for E&S in CF patients with F508del-CFTR mutation 6-<12y
12. R DB PC for E&S in CF patients with F508del-CFTR mutation 11 - < 18y (and adults)
13. Rollover OL long-term S&E in CF patients with F508del-CFTR mutation 6 - y (and adults)
14. PK/PD in CF patients with F508del-CFTR mutation 0 - < 6 y
15. Relative bioavailability to characterize PK of the ped age appropriate formulation relative to the tablet formulation in healthy adults.